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Adjunctive herbal medicine therapy for inflammatory bowel disease: a systematic review and meta-analysis

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ABSTRACT

Introduction:

We conducted a systematic review and meta-analysis to evaluate the evidence on herbal medicine for inducing or maintaining remission in ulcerative colitis (UC) and Crohn's disease (CD).

Methods:

Eight databases were searched up to January 2017 for randomised controlled trials of herbal medicine as an adjunct to conventional medication in patients with IBD. Data were extracted to obtain risk ratio (RR) of failure of inducing or maintaining remission, with 95% confidence intervals (CI). Risk of bias was assessed using the Cochrane criteria.

Results:

Twenty-nine RCTs (24 UC, 5 CD) were included. In UC, herbal medicine was superior to placebo for clinical remission (RR of remission failure = 0.74, 95% CI: 0.59-0.93; I^2 = 62%) and maintaining remission (RR of failure to maintain remission = 0.34, 95% CI: 0.17-0.67; I^2 = 0%). Traditional Chinese patent medicine with standard therapy reduced the risk of no comprehensive remission by 19% compared to standard therapy alone (RR of no remission = 0.81, 95% CI: 0.70-0.95; I^2 = 0%). In CD, however, the effect of herbal medicine was significant neither for inducing nor maintaining remission (RR of remission failure = 0.57, 95% CI: 0.24-1.33; I^2 = 87%; RR of failure to maintain remission = 0.95, 95% CI: 0.60-1.52). Few serious adverse events were reported.

Conclusions:

An adjunctive herbal medicine to standard therapy appears effective with few adverse events in achieving and maintaining remission in UC, while there is a lack of supporting evidence for CD. Future high quality trials are warranted.

Key words: Inflammatory bowel disease, ulcerative colitis, Crohn's disease, herbal medicine, systematic review

Abbreviations: IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CAM, complementary and alternative medicine; RCTs, randomised controlled trials; TCPM, traditional Chinese patent medicine; AEs, adverse events; DAI, disease activity index.

BACKGROUND

Inflammatory bowel disease (IBD), where two principal types are Crohn's disease (CD) and ulcerative colitis (UC), is characterised by a chronic inflammatory state of intestinal mucosa caused by dysfunction of the gastrointestinal (GI) immune system[1]. The distinguishing point between CD and UC is that CD is a transmural inflammatory disease that can affect any of the entire GI tract, whereas UC is a non-transmural inflammatory disease that affects only colon and rectum[2]. The incidence and prevalence of UC and CD have been prominent in western countries, however, recently the gradual increase in the incidence of UC has also been observed in developing countries[3]. Considering the trend that the occurrence of UC preceded that of CD by about 10 years, it is expected that the incidence of CD would also eventually increase[3].

IBD causes not only symptoms such as diarrhoea with stool containing mucus or blood, abdominal pain, and fever[1], but also complications from anaemia[4] to colorectal cancer[5]. In a majority of cases, the disease course of UC and CD is characterised by a sequence of flare-up episodes followed by remission periods[3], in other words, the alternation of active period and quiescent period. Thus, the treatment focuses on the induction of remission when the disease is active, and the maintenance of achieved remission[6, 7]. It depends on the extent and the severity of the disease, for example, patients with UC can be treated with medications from topical or oral 5-aminosalicylic acids (5-ASA) and steroids to thiopurines and anti-tumour necrosis factor (TNF) agents[7, 8], while patients with CD can be treated with drugs from budesonide or with systemic corticosteroids to anti-TNF agents[6]. Nevertheless, there are marked inter-individual and perhaps even intra-individual differences in treatment responses that are currently unpredictable for the

most part[9, 10].

Due to the desire to avoid long-term medications and the fear of side effects[11], a number of IBD patients, clinicians, and researchers are paying more attention to complementary and alternative medicine (CAM). In North American and European studies, the current or past use of CAM to treat IBD ranges from 21-60%[11]. In IBD patients, herbal medicine in particular is the most preferred CAM intervention[12]. Several reasons for the high prevalence of herbal medicine use in this population may include a lack of perceived therapeutic response to standard therapy, increased recognition of adverse events (AEs) associated with medication while herbal medicine is generally considered safe or at least not recognised to cause serious side effects, and patients' gaining a sense of control over their disease and management of symptoms[11, 12].

While several systematic reviews and meta-analyses on CAM and herbal medicine for IBD were performed[13-15], the evidence is inconclusive and limited due to language restriction. Because of the prevalent use of herbal medicine, the information concerning the efficacy and safety of it is important for both patients and clinicians. We have therefore performed a systematic review and meta-analysis to critically evaluate the effectiveness and safety of herbal medicine in both induction and maintenance of remission in UC and CD.

METHODS

The review process followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[16].

Search strategy

A literature search was conducted using the following medical databases from inception to January 2017 without language restrictions: PubMed, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), AMED (Allied & Complementary Medicine Database), CNKI (China National Knowledge Infrastructure), KMBASE (Korean Medical Database), NDSL (National Digital Science Library), and OASIS (Oriental Medicine Advanced Searching Integrated System). The following key words as free texts and MeSH (medical subject headings) terms were used for building search strategies: inflammatory bowel disease(s); Crohn('s) disease(s); ulcerative colitis; Chinese traditional medicine; Chinese herbal drug(s); medicinal plant(s); plant extract(s); and phytotherapy. The key words were transformed considering the feature of each database (e.g. types of field or principal language) and combined with the filters for randomised controlled trials only. For PubMed, the following strategy was applied: ((("Colitis, Ulcerative"[MeSH] OR ulcerative colitis OR "Crohn Disease"[MeSH] OR Crohn* OR "Inflammatory Bowel Diseases"[MeSH] OR "inflammatory bowel disease" OR IBD) AND (Korean traditional medicine OR Chinese traditional medicine OR Chinese medicine [tiab] OR oriental traditional medicine OR east asian traditional medicine OR Kampo medicine OR phytotherapy OR Chinese herb* OR herbal drug* [tw] OR herbal medicine OR medicinal plant* OR herbal OR herbals OR herbalism))) AND (singl* OR doubl* OR tripl* OR trebl* OR blind* OR mask* OR placebo* OR single-blind* OR double-blind* OR triple-blind* OR random* OR (controlled clinical)). In

addition, we also hand-searched the reference lists of relevant articles.

Eligibility criteria

We selected randomised controlled trials (RCTs) evaluating the efficacy of herbal medicine for the adjuvant treatment of IBD in adult patients (aged ≥ 18 years) who were diagnosed with UC or CD as defined in the original articles. Considering herbal medicine is usually taken in combination with conventional therapies, we included RCTs comparing herbal medicine with placebo or herbal medicine as an adjuvant therapy with conventional medicine if the identical types and dosages of medications were applied in both groups. Trials aiming to induce remission in an active period and maintain remission in a quiescent period were both included.

We followed the definition of herbal medicine from 'General guidelines for methodologies on research and evaluation of traditional medicine' by World Health Organisation (WHO)[17]. As we sought RCTs comparing herbal medicine with placebo or herbal medicine used as an adjuvant therapy with conventional medicine, RCTs comparing herbal medicine alone with conventional medicine or no treatment were excluded. For a trial with more than two arms, only arms meeting the inclusion criteria were included in the analysis. The extent of Chinese herbal drugs was defined according to the 'Provisions for Drug Registration' by Chinese Food and Drug Agency (CFDA, available at http://eng.sfda.gov.cn/WS03/CL0768/61645.html). Within the extent, we only considered traditional Chinese patent medicine (TCPM) of which the total components were available and that were tested and listed in the CFDA and the Pharmacopoeia of the People's Republic of China (2010 edition). Additionally, considering pharmacokinetics differs by the route of

administration, we restricted the method of application to oral administration only, thus, injections or suppositories were excluded.

Regarding outcome measures, only studies reporting on clinical outcomes of achieving or maintaining clinical remission were included. Studies reporting comprehensive remission consisting of a combination of clinical and endoscopic remission were also considered. We included studies that provided the definition of clinical or comprehensive remission. Although there was no limitation regarding the type of data - dichotomous or continuous - , only studies reporting on the induction or the maintenance of clinical or comprehensive remission as a form of dichotomous data, e.g. the proportion of patients who achieved or maintained clinical or comprehensive remission, were included in the meta-analysis. For the articles published in Chinese that did not use the term “remission”, the definition of remission followed the Consensus on the diagnosis and management of UC developed by the European Crohn's and Colitis Organisation (ECCO)[18], stating that ‘complete resolution of symptoms and endoscopic mucosal healing’. In addition, AEs were summarised and tabulated.

Study selection

Two authors (S. Kim and B.-H. Lee) independently searched articles and made a list of retrieved articles in a Microsoft excel sheet. Two authors (B.-H. Lee and X. Zhang) searched Chinese databases and another (S. Lee) checked the list of retrieved articles. After overlapping studies were removed, articles were screened based on their title and abstract. Full texts of the retrieved articles then were collected and reviewed by three authors (S. Kim, B.-H. Lee, and S. Lee) in order to select the articles meeting the inclusion criteria. When a

discrepancy between the authors occurred, it was resolved by discussion with the corresponding author. The basic information on finally selected articles was tabulated. The variables extracted were year of publication, country, type of IBD and disease states, sample size, herbal medicine group intervention, control group intervention, outcomes including percentage of patients achieving or maintaining remission, and AEs.

Risk of bias assessment

Risk of bias assessment was conducted based on the Cochrane Collaboration's risk of bias assessment tool, which consists of following 7 items related to the biases that could affect the outcomes: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other bias[19]. Each article was assessed and classified as one of the following three categories for each item: high risk; low risk; or unclear risk. Three authors (S. Kim, X. Zhang, and H. Lee) independently assessed each article according to the criteria and had a discussion to resolve the disagreements.

Data syntheses and statistical analyses

Statistical analyses and visualisations were conducted using the Review Manager programme (RevMan, version 5.1 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark). Studies were combined according to the type of IBD (i.e. UC or CD), and/or outcome measures. The primary outcome of interest was the percentage of patients who achieved or maintained clinical or comprehensive remission, depending on the disease state (i.e. active or quiescent). The secondary outcomes included disease activity index (DAI) and

AEs associated with herbal medicine. The impact of herbal medicine on binary outcomes such as clinical remission at the end of treatment were expressed as risk ratio (RR) with 95% confidence intervals (CI), while continuous outcomes such as DAI were expressed as mean difference (MD) or standardised mean difference (SMD) with 95% CI. Data were pooled in a random effects model with inverse variance method as clinical characteristics of the studies were expected to be highly variable (e.g. disease state, treatment duration, outcome assessment time point).

A chi-squared test was used to assess heterogeneity, with a significance level of $P < 0.1$. To evaluate inconsistencies among trials, the I^2 statistic was used. The I^2 statistic indicates the proportion of variability among studies not explained by chance alone. The value of I^2 statistic > 50% was considered to indicate substantial heterogeneity[20, 21]. The small study effect (i.e. a tendency for estimates of the intervention effect to be more beneficial in smaller studies) was also assessed with funnel plots when the analyses included more than 10 studies[22].

We performed sensitivity analyses to evaluate whether the findings were affected if studies with a high/unclear risk of bias for randomisation and/or allocation concealment were excluded from pooling[23, 24]. As a subgroup analysis, we also explored the effect of TCPM as an adjunct to conventional medication as they usually contain multiple herbs and may produce different effects from single herbs. All these analyses are observational by nature and the results were interpreted accordingly[20].

RESULTS

Study selection

A total of 3050 studies were identified through our searching. After 266 overlapping studies were removed, 2784 remaining articles were screened and 2254 studies were excluded based on the title and abstract. Subsequently, an assessment on the full-texts of 530 remaining studies was conducted. Of these, 501 studies were excluded for the following reasons; 470 did not meet the inclusion criteria; 7 did not report on the name of medications specifically; 10 did not report relevant clinical outcomes; and 14 overlapped. Finally, 29 studies were finally included in this review and the process following PRISMA statement is depicted in Figure 1[16]. Of these, 24 studies (n=1,847) were about UC[25-48], while 5 studies (n=323) were on CD[49-53].

Study characteristics

A total of 1,847 patients were involved in the studies of UC, with a sample size ranging from 20 to 224. Fourteen studies investigated the induction of remission for patients in active state[25, 27-35, 38, 40, 42, 45], four investigated the maintenance of remission in quiescent state[26, 41, 46, 48], and one study investigated both[47]. For the remaining five studies which did not clearly specify the disease state[36, 37, 39, 43, 44], an active state was assumed based on their inclusion criteria. Regarding the intervention, 12 studies[26, 28, 29, 31, 34, 35, 41, 42, 45-48] investigated on the efficacy of single herbal drugs, such as *Punica granatum* peel extract syrub[29], silymarin (silybummarianum seed extract)[26], curcumin[28, 41], HMPL-004 (*Andrographis paniculata* ethanol extract, Indian echinacea)[34], Polyphenon E capsules containing (-)-epigallocatechin-3-gallate (EGCG), the

most prevalent polyphenols in green tea leaves[35], GWP42003 (hard gelatin capsule containing cannabidiol and Δ^9-tetrahydrocannabinol extracted from *Cannabis sativa* L.)[31], aloe vera gel[42], wheat grass juice[45], evening primrose oil[47], Vi-Siblin Ⓢ S granules containing *Plantago ovata* (Ispaghula) husk[48] and *Plantago ovata* seeds[46]. Apart from one study of *Plantago ovata* seed which was compared with mesalazine[46], the other 11 studies used a placebo control. Meanwhile, the other 12 studies[25, 27, 30, 32, 33, 36-40, 43, 44] were on TCPM and they were all published in Chinese language journals. Of these, four trials were on Chang yu ning granule, a combination of various herbs like *Coptis Japonica*, *Scutellaria baicalensis*, *Pulsatilla chinensis*, and Halloysite[27, 32, 33, 38]. Another three trials were on Bu pi yi chang pill consisting of *Astragalus membranaceus*, *Codonopsis pilosula*, *Aucklandia lappa* and *Corydalis turtschaninovii*, etc.[36, 37, 44]. The other five trials were on Kui jie ling granule[30, 40], Gu chang zhi xie wan[25], Chang yan ning syrup[39], and Yunnan Bai yao capsule[43], respectively. The duration of UC treatment varied from one to 12 months (median 2 months). Among the 19 studies reporting the induction of remission, six studies calculated the proportion of patients who achieved clinical remission defined by Simple Clinical Colitis Activity Index (SCCAI)[54], Mayo score[55], UC disease activity index[56] or Suggestion on diagnosis and treatment of UC in integrated Chinese and Western Medicine[57], respectively. Two studies reported the proportion of patients who achieved comprehensive remission defined by Chinese national guidelines of diagnosis and treatment of IBD[58, 59], whereas other two studies used author-defined criteria which were not specifically reported. The other six studies reported only changes of clinical score or the number of improved patients, so they were not put in the statistical pooling. Four

studies on the maintenance of remission in UC all reported relapse of disease activity (Table 1).

Five studies involved total 323 patients with CD. Of these, three studies compared herbal medicine such as Boswelan (*Boswellia serrata* resin extract, Indian frankincense[50], HMPL-004[51], and SedaCrohn®(*Artemisia absinthium* powder, wormwood)[53] to placebo. The other two studies examined the effectiveness of herbal medicine without a placebo. Of them, one was on SedaCrohn®[52], and the other was on Shen ling bai zhu wan, TCPM[49]. All except one study[50] investigated the induction of remission in active state. The CD study duration ranged from 1.5 to 12 months (median 2 months) (Table 2).

Risk of bias assessment

For two studies published as a form of conference abstract [31, 51], items that were not fully reported were rated as 'unclear'. Nine of the included studies (31.0%) described the appropriate method of random sequence generation such as a random number table[25, 26, 32] or computer-generated randomisation sequence[29, 35, 41, 42, 46, 50] and only six studies (20.7%) adequately concealed group allocation[29, 34, 41, 45, 46, 50]. For blinding of participants and personnel, 15 studies which tested herbal medicine as an adjunct to conventional medication against conventional medication alone were considered as having a high risk of bias[25, 27, 30, 32, 33, 36-40, 43, 44, 46, 49, 52] while all the placebo-controlled studies were given a low risk of bias except one study using a placebo not identical to verum[47]. For blinding of outcome assessment, studies reporting outcome measures evaluated by unblinded participants and/or physicians considered unlikely to have been blinded were given a high risk of bias[25, 27, 30, 32, 33, 36-40, 43, 44, 46, 49, 52]. On

attrition bias, studies which did not adopt intention-to-treat analyses were considered as having a high risk of bias. Regarding other sources of bias, 16 studies that neither appropriately describe random sequence generation nor allocation concealment methods, were given an unclear risk of bias[27, 28, 30, 33, 36-40, 43, 44, 47-49, 52, 53]. In addition, one study was rated as having a high risk of bias[45], because the numbers in the result table were not consistent. The summary and the supporting information for risk of bias assessment are provided in Figure 2 and Table S1.

Effectiveness of herbal medicine

UC (24 studies)

A total of seven studies assessed the achievement of clinical remission[28, 31, 34, 35, 38, 40, 42]. Five placebo-controlled studies testing GWP42003[31], curcumin[28], HMPL-004[34], Polyphenon E capsules[35] and aloe vera[42] reduced the risk of failure to achieve clinical remission in active UC to 74% of what it would have been, but a substantial heterogeneity was detected (five studies, RR of failure to achieve clinical remission 0.74, 95% CI [0.59, 0.93]; $\chi^2 = 10.49$, P = 0.03; $I^2 = 62\%$) (Figure 3a). When we restricted our analysis to trials with adequate randomisation and/or allocation concealment[34, 35, 42], the benefit remained significant (three studies, RR of failure to achieve clinical remission 0.79, 95% CI [0.66, 0.95]; $\chi^2 = 2.56$, P = 0.28; $I^2 = 22\%$). However, two trials[38, 40] testing TCPM combined with standard therapy against standard therapy alone did not find significant difference in achieving clinical remission in active UC (two studies, RR of failure to achieve clinical remission 0.87, 95% CI [0.74, 1.03]; $\chi^2 = 0.07$, P = 0.79; $I^2 = 0\%$) (Figure 3b).

Regarding the four studies reporting on comprehensive remission[36, 37, 43, 44], the meta-analysis demonstrated that herbal medicine significantly reduced the risk of failure to achieve remission by 45% (four studies, RR of failure to achieve comprehensive remission 0.81, 95% CI [0.70, 0.95]; $\chi^2 = 0.95$, P = 0.81; $I^2 = 0\%$) (Figure 3c). All of them compared TCPM combined with standard therapy with standard therapy alone: three tested Bu pi yi chang pill[36, 37, 44] and one was on Yunnan Bai yao capsule[43]. A sensitivity analysis was not performed as none of these four studies were given low risk of bias for adequate randomisation or allocation concealment.

In three studies reporting maintenance of remission[26, 41, 46], compared with a placebo, herbal medicine such as silymarin[26] and curcumin[41], maintained remission of quiescent UC up to six months (two studies, RR of failure to maintain remission 0.34, 95% CI [0.17, 0.67]; $\chi^2 = 0.25$, P = 0.62; $I^2 = 0\%$) (Figure 3d) but *Plantago ovata* seeds[46] added to standard therapy failed to do so (RR of failure to maintain remission 0.85, 95% CI [0.42, 1.72], P = 0.65). They all had low risk of bias for adequate random sequence generation/allocation concealment.

The remaining ten studies that were not reporting remission data provided clinical score changes or the number of patients with any symptom improvements[25, 27, 29, 30, 32, 33, 39, 45, 47, 48]. Of these, four studies were on single herbal medicine: in the study of *Punica granatum* peels, there was no significant difference of clinical response rate between treatment group and placebo group although the rate was higher in the treatment group (41.4% vs. 18.2%, P=0.055)[29]. In contrast, the wheat grass juice study demonstrated a significant improvement of DAI score in the treatment group compared to a placebo group (10 of 11 patients were improved in the treatment group vs. 5 of 12 in the control

group)[45]. Greenfield et al. tested the efficacy of evening primrose oil against a placebo: a significantly improved stool consistency was observed compared to a placebo, however, there was no significant difference in stool frequency and rectal bleeding[47]. Furthermore, a cross-over study on *Plantago ovata* husk showed the significantly higher improvement rate in treatment group (69% vs. 24%, $P < 0.001$)[48]. The other six studies were on TCPM added to standard therapy[25, 27, 30, 32, 33, 39]. Two studies investigating on Chang yu ning evaluated the changes of DAI score that were significantly improved in TCPM plus standard therapy group compared to standard therapy alone[32, 33]. The other four studies of Chang yan ning syrup/granule[27, 39], Gu chang zhi xie wan[25], and Kui jie ling granule[30] reported that significantly more patients reported improvement in the combination group compared to standard therapy group (four studies, RR of failure to achieve any improvement 0.35, 95% CI [0.21, 0.59]; $\chi^2 = 1.18$, $P = 0.76$; $I^2 = 0\%$).

CD (5 studies)

Three studies compared herbal medicine with a placebo[50, 51, 53]. Of these, HMPL-004 and SedaCrohn® failed to reduce the risk of failure to achieve clinical remission (two studies, RR of failure to achieve clinical remission 0.57, 95% CI [0.24, 1.33]; $\chi^2 = 7.67$, $P = 0.006$; $I^2 = 87\%$)[51, 53] (Figure 4a). A sensitivity analysis was not conducted as it was not clear whether these two studies reported adequate randomisation/allocation concealment method. The other one study comparing Boswelan with a placebo also failed to maintain remission in quiescent CD (RR of failure to maintain remission 0.95, 95% CI [0.60, 1.52])[50] (Figure 4b).

The other two studies compared herbal medicine given with conventional medicine to conventional medicine alone[49, 52]. One study found that SedaCrohn® was effective to

achieve clinical remission (RR of failure to achieve clinical remission 0.25, 95% CI [0.07, 0.90])[52], whereas another study on TCPM, Shen ling bai zhu wan, did not (RR of failure to achieve clinical remission 0.74, 95% CI [0.54, 1.02])[49].

Safety

Twenty-two of 29 studies (75.9%) reported AEs[25-30, 32-35, 38, 39, 41, 42, 44-46, 48-52]. A total of 314 cases of AEs associated with herbal medicine were reported in 19 studies[25-30, 34, 35, 38, 39, 41, 42, 44-46, 48-51] and 3 studies reported that no AEs had occurred[32, 33, 52]. Of these, 280 cases (89.1%) were reported in 12 studies on single herbal medicine such as *Punica granatum* peel extract syrub[29], silymarin[26], curcumin[28, 41], HMPL-004[34, 51], Polyphenon E capsules[35], aloe vera gel[42], wheat grass juice[45], Vi-Siblin Ⓢ S granules[48], Boswelan[50], and *Plantago ovata* seeds[46], while seven studies on TCPM such as Gu chang zhi xie wan[25], Chang yu ning granule[27, 38], Kui jie ling granule[30], Chang yan ning syrup[39], Bu pi yi chang pill[44] and Shen ling bai zhu wan[49] only reported 34 cases (10.9%). Most frequently reported AEs were GI symptoms like abdominal pain, nausea and vomiting, GI discomfort, diarrhoea or constipation. No study showed a significantly higher risk of AEs associated with herbal medicine than conventional medication, and eight studies reported that standard treatment had more AEs than adjuvant herbal medicine treatment[25, 30, 33, 38, 44, 48-50] (Table S2).

DISCUSSION

Summary of main findings

This systematic review and meta-analysis has summarised the currently available evidence for the effectiveness and the safety of various herbal medicines for achieving or maintaining remission in UC and CD. Out of 29 included studies in our review (24 UC and 5 CD), 16 studies reporting clinical or comprehensive remission contributed data to the meta-analysis.

Single herbal medicines such as GWP42003, curcumin, HMPL-004, Polyphenon E capsules and aloe vera, appear more effective in achieving clinical remission in active UC compared with placebo, but TCPM in combination with sulfasalazine did not help achieve clinical remission of UC compared with sulfasalazine alone. Additional TCPM treatments to standard therapy were effective in inducing endoscopic as well as clinical remission in UC. For maintaining remission in quiescent UC, herbal medicines such as silymarin and curcumin were also effective. However, in CD, herbal medicines failed to achieve and maintain clinical remission. For safety, AEs associated with herbal medicine were mostly GI symptoms and few serious AEs were reported. The reported incidence of AEs has been similar between herbal medicine plus conventional medication group and conventional medication only group.

Applicability of the evidence

Herbal medicine is one of the most widely used CAM modalities in IBD patients[12, 60]. Several reasons for the high prevalence of herbal medicine use in this population may include a lack of perceived therapeutic response to standard therapy, increased recognition

of AEs associated with medication while herbal medicine is generally considered safe or at least not recognised to cause serious side effects, and gaining a sense of control over their disease and management of symptoms[61]. With the increase in IBD patients' use of and researchers' interests in herbal medicine, a number of clinical studies on herbal medicine for IBD have been conducted and accordingly, several systematic reviews and meta-analyses were published[13-15]. One meta-analysis concluded that herbal medicine demonstrated a promising effect for the induction of clinical remission, but a small number of heterogeneous studies made it difficult to draw convincing evidence[15]. Although our results broadly corroborate previous reviews, they included studies on single herbal medicine published mostly in English and German only. In other words, trials of Chinese herbal medicine have not been evaluated. Our systematic review is the first qualitative and quantitative analysis that included both studies on single herbal medicine and Chinese herbal medicine as an adjunct to conventional medication.

There are several distinctive features of our systematic review. Traditional Chinese medicine or traditional East-Asian medicine has long taken a part in healthcare and been commonly utilised as a complementary or adjunctive treatment along with conventional medication in Asian countries including China, Japan, and Korea[1, 62]. However, because most of the studies on Chinese herbal medicine were published in Chinese, researchers have experienced difficulties in accessing and interpreting them. Our review could give researchers and clinicians new information on the efficacy and safety of complementary treatment of Chinese herbal medicine for IBD. Among innumerable Chinese herbal medicines for IBD, we only considered TCPM in our review because unlike other Chinese herbal medicines, TCPM has been scientifically tested and validated therefore, widely

accepted and recommended by the CFDA. Additionally, we only included RCTs testing herbal medicine in conjunction with standard therapy because such practice is common in China and other East Asian countries, and we also considered it unusual or unlikely to achieve clinical response/remission with herbal medicine alone in other western countries as well.

Risk of bias in the included studies

Although our analysis indicates the possible benefit from herbal medicine for achieving clinical/endoscopic remission in IBD, careful interpretation of the results is necessary mainly due to high risk of bias in the included trials.

It is well known that studies failing to report the method used to generate the randomisation sequence or to conceal group assignment tend to overestimate the effect of intervention under investigation[63, 64]. When we limited our analyses to studies which reported adequate randomisation and/or allocation concealment, the results were similar: herbal medicine reduced the risk of failure to achieve clinical remission by 26% and 21%, respectively. However, the number of studies becomes only three, making the evidence more limited. Moreover, only two out of 13 Chinese studies reported an adequate method of random number generation[25, 32] and allocation concealment was not mentioned in any of them. A recent research raised concern that Chinese trials were labelled as randomised, but in fact they might not be truly randomised[65]. The strength of the evidence in our review then could be weakened due to possible selection bias.

Regarding blinding, only a quarter of the included studies secured blinding of participants and outcome assessment, which could directly lead to higher risk of performance and detection biases. We may have applied too strict a rule in evaluating the

risk of bias for outcome assessment blinding as we gave unclear risk of bias if a trial adopted outcome measures evaluated by unblinded participants and/or physicians whose blinding status was not clearly reported in the article. Nevertheless, the reason why more than a half of the studies (n = 15) failed to blind both participants and outcome assessment is probably the study design itself. All 15 trials compared herbal medicine plus standard therapy with standard therapy alone, i.e. A + B vs. B design. This type of design can be a down-to-earth approach on the one hand but also exaggerate the treatment effect on the other as a placebo effect cannot be controlled properly. All these should be considered if we are to adequately interpret the present results.

Limitations of this review

There are several limitations to our study. Probably the main weakness of this review arises from the quality of the included studies, with only 37.9% of the included studies reporting adequate randomisation and allocation concealment, and approximately a quarter of them being double-blinded. Rough reporting of AEs should also be considered when evaluating the overall benefit and harm. As conclusions of systematic reviews and meta-analyses are often limited by the quality of the primary studies, our review findings are not free from 'garbage in, garbage out' problems.

Language restrictions in systematic reviews may have different impact on the results depending on the intervention of interest belongs to mainstream medicine or CAM[66]. Despite our extensive literature search without language restriction and inclusion of theses, we may have missed relevant studies, or this may reflect on the contrary, relatively small amount of data available in this field. While our findings show possible benefit of herbal

medicine for inducing clinical/endoscopic remission in IBD and this is consistent with the results from previous reviews[13-15], we had only 16 studies in our meta-analysis and three studies on CD. Therefore, the present findings mainly concern with UC and further high-quality studies are warranted since SedaCrohn® demonstrated a potential for inducing clinical remission in active CD[52, 53].

It is of note that the included studies were quite heterogeneous: each used different diagnostic criteria, a range of herbal medicine interventions and control types, and different outcome measures. We could not analyse how patient responses vary at different time points during the treatment period which might have been clinically informative. The most studied herbal medicine was tested in four RCTs at most. This may explain why previous reviews performed only qualitative analyses. We could not explore any sources of heterogeneity via subgroup analysis as there were only a small number of studies. Promising results in our review should be reproduced in future rigorous studies, e.g. curcumin, aloe vera gel, or Bu pi yi chang pill for clinical/endoscopic remission in active UC or SedaCrohn® for clinical remission for active CD.

Lastly, we only included Chinese trials of TCPMs in our review. Because the quality of Chinese herbal medicine could be influenced by a number of environmental factors[67], only TCPMs of which the ingredients are standardised and validated were considered. As there is an enormous variety of Chinese herbal medicine and its application also varies to a large extent, we believe that looking at the evidence from TCPMs can be a good starting point of Chinese herbal medicine research.

CONCLUSIONS

To conclude, published evidence suggests that an adjunctive herbal medicine treatment to standard therapy appears effective in inducing and maintaining remission in active and quiescent UC with few side effects. There is a lack of supporting evidence on herbal medicine as a complementary therapy for inducing and maintaining remission in CD. Future trials of herbal medicine as an adjunct to conventional medication are warranted to replicate the benefit in UC.

Author contributions

All research was done by the authors. Lee B-H and Lee H developed the study concept and protocol. Kim S, Lee B-H, X. Zhang, Lee S, and Lee H performed literature searching, data extraction, and risk of bias assessment. Kim S and Park J-W conducted analyses and wrote the manuscript. Lee H coordinated the project, resolved disagreements on inclusion, exclusion, risk of bias assessment of included studies, double-checked analyses, and critically edited the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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FIGURE CAPTIONS

Fig. 1. PRISMA flow diagram of literature search[21].

PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Fig. 2. Risk of bias summary of the included studies.

+ indicates low risk of bias; -, high risk of bias; ?, unclear risk of bias[15].

Fig. 3. Forest plot of randomised controlled trials of herbal medicine added to standard therapy in UC.

(a), Herbal medicine vs. placebo for inducing clinical remission in active UC; (b), TCPM added to standard therapy vs. standard therapy for inducing clinical remission in active UC; (c), TCPM added to standard therapy vs. standard therapy for inducing comprehensive remission in active UC; (d), Herbal medicine vs. placebo for maintaining remission in quiescent UC; UC, ulcerative colitis; M-H, Mantel-Haenszel; TCPM, traditional Chinese patent medicine.

Fig. 4. Forest plot of randomised controlled trials of herbal medicine added to standard therapy in CD.

(a), Herbal medicine vs. placebo for inducing clinical remission in active CD; (b), Herbal medicine vs. placebo for maintaining clinical remission in quiescent CD; CD, Crohn's disease; M-H, Mantel-Haenszel.

Table 1. Characteristics of the included studies of herbal medicine for UC

Author (year) Country	No. of patients	Disease state	Intervention	Control	Duration of therapy (months)
Herbal medicine vs. placebo					
Kamali (2015)[29] Iran	78	Active	1) *Punica granatum* peel aqueous extract syrup, 8 cc, twice a day 2) Standard therapy	1) Placebo 2) Standard therapy	1
Rastegarpanah (2015)[26] Iran	80	Quiescent	1) Silymarin (Silybummarianum seed extract) tablets, 140 mg, once a day 2) Standard therapy	3) Placebo 4) Standard therapy	6
Lang (2015)[28] Israel, Hong Kong, and Cyprus	50	Active	1) Curcumin capsules, 3 g, twice a day 2) Mesalazine, dose optimised, oral and topical	1) Placebo 2) Mesalazine, dose optimised, oral and topical	1
Irving (2015)[31] UK	60	Active	1) GWP42003 (hard gelatin capsule containing cannabidiol and Δ^9-tetrahydrocannabinol extracted from *Cannabis sativa* L.), 0.5 g, twice a day 2) Standard therapy	1) Placebo 2) Standard therapy	2.5
Dryden (2013)[35] US	20	Active	1) Polyphenon E capsules containing (-)-epigallocatechin-3-gallate (EGCG), 400 mg or 800mg, twice a day 2) Standard therapy	1) Placebo 2) Standard therapy	2
Sandborn (2013)[34] US, Canada, Germany, Romania, and Ukraine	224	Active	1) HMPL-004 (*Andrographis paniculata* ethanol extract, Indian echinacea), 1.2 g or 1.8 g, three times a day 2) Mesalazine, stable dose	1) Placebo 2) Mesalazine, stable dose	2
Hanai (2006)[41] Japan	89	Quiescent	1) Curcumin, 1 g, twice a day 2) Sulfasalazine or mesalazine, dose individualised	1) Placebo 2) Sulfasalazine or mesalazine, dose individualised	6
Langmead (2004)[42]	44	Active	1) Aloe vera gel, 100 ml, twice a day	1) Placebo	1

UK			2)	Standard therapy	2) Standard therapy	
Ben-Arye (2002)[45] Israel	23	Active	1) 2)	Wheat grass juice, 100 ml, once a day (starting with 20 ml and increasing by 20 ml each day until 100 ml) Standard therapy not specified	1) Placebo (starting with 20 ml and increasing by 20 ml each day until 100 ml) 2) Standard therapy not specified	1
Greenfield (1993)[47] UK	27	Active and quiescent	1) 2)	Evening primrose oil, 250 mg*12 capsules (1 month) followed by 6 capsules (5 months), daily Standard therapy	1) Olive oil placebo, 1 g*12 capsules (1 month) followed by 6 capsules (5 months), daily 2) Standard therapy	6
Hallert (1991)[48] Sweden	36	Quiescent	1) 2)	Vi-Siblin^{S} S granules (containing 3.52 g of Ispaghula husk), 8 g, twice a day Standard therapy	1) Placebo 2) Standard therapy	2
Herbal medicine as an add-on to active medication vs. active medication alone						
Liu (2016)[25] China	140	Active	1) 2)	Gu chang zhi xie wan, 4 g, three times a day Compound glutamine enterosoluble capsules, 3 capsules, three times a day	Compound glutamine enterosoluble capsule, 3 capsules, three times a day	1.5
Jia (2015)[30] China	160	Active	1) 2)	Kui jie ling granule, 5 g, three times a day Sulfasalazine, 1 g, four times a day	Sulfasalazine, 1 g, four times a day	3
Li (2015)[27] China	41	Active	1) 2)	Chang yu ning granule, 10 g, twice a day Mesalazine, 1 g, four times a day	Mesalazine, 1 g, four times a day	2
Lin (2014)[32] China	60	Active	1) 2)	Chang yu ning granule, 10 g, twice a day Mesalazine, 1 g, four times a day	Mesalazine, 1 g, four times a day	1
Wang (2013)[33] China	60	Active	1) 2)	Chang yu ning granule, 10 g, twice a day Mesalazine, 1 g, four times a day	Mesalazine, 1 g, four times a day	1
Jiang (2011)[36] China	218	(Likely) active	1) 2)	Bu pi yi chang pill, 6 g, three times a day Sulfasalazine, 1 g, four times a day	Sulfasalazine, 1 g, four times a day	2
Shen (2010)[37] China	56	(Likely) active	1) 2)	Bu pi yi chang pill, 6 g, three times a day Balsalazide, 2.25 g, three times a day	Balsalazide, 2.25 g, three times a day	3
Shi (2009)[38] China	44	Active	1) 2)	Chang yu ning granule, 10 g, twice a day Sulfasalazine, 1 g, three times a day	Sulfasalazine, 1 g, three times a day	2
Chang (2007)[40] China	60	Active	1) 2)	Kui jie ling granule, 5 g, three times a day Sulfasalazine, 1 g, four times a day	Sulfasalazine, 1 g, four times a day	12

Wu (2007)[39] China	92	(Likely) active	1) 2)	Chang yan ning syrup, 20 ml, three times a day Sulfasalazine, 1 g, four times a day	Sulfasalazine, 1 g, four times a day	2
Wang W (2003)[44] China	60	(Likely) active	1) 2)	Bu pi yi chang pill, 6 g, three times a day Sulfasalazine, 1 g, four times a day	Sulfasalazine, 1 g, four times a day	1
Wang X (2003)[43] China	56	(Likely) active	1) 2)	Yunnan Bai yao capsule, 0.5 g, four times a day Sulfasalazine, 2 g, three times a day	Sulfasalazine, 2 g, three times a day	1
Fernández-Bañares(1999)[46] Spain	69	Quiescent	1) 2)	*Plantago ovata* (Desert Indian wheat) seeds, 10 g, twice a day Mesalazine, 500 mg, three times a day	Mesalazine, 500 mg, three times a day	12

UC, ulcerative colitis.

Table 2. Characteristics of the included studies of herbal medicine for CD

Author (year) Country	No. of patients	Disease state	Intervention	Control	Duration of therapy (months)
Herbal medicine vs. placebo					
Holtmeier (2011)[50] Germany	82	Quiescent	Boswelan (*Boswellia serrata* resin extract, Indian frankincense), 400 mg*2 capsules, three times a day	Placebo	12
Sandborn (2010)[51] Us and Ukraine	101	Active	1) HMPL-004, 1200 mg a day 2) Standard therapy	1) Placebo 2) Standard therapy	2
Omer (2007)[53] Germany	40	Active	1) SedaCrohn® (*Artemisia absinthium* powder, wormwood), 400 mg*3 capsules, twice a day 2) Corticosteroids, dose individualised	3) Placebo 4) Corticosteroids, dose individualised	2.5
Herbal medicine as an add-on to active medication vs. active medication alone					
Zheng (2015)[49] China	80	Active	1) Shen ling bai zhu wan, 6 g, twice a day 2) Methotrexate injection, 5-10 mg, twice a week followed by folic acid injection or p.o., 6-12 mg	Methotrexate injection, 5-10 mg, twice a week followed by folic acid injection or p.o., 6-12 mg	2
Krebs (2010)[52] Germany	20	Active	1) SedaCrohn® (*Artemisia absinthium* powder, wormwood), 400 mg*3 capsules, three times a day 2) Standard therapy	Standard therapy	1.5

CD, Crohn's disease; p.o., per os.

SUPPLEMENTARY MATERIALS

Supplementary file 1: **Table S1.** Supporting information for risk of bias assessment.

Supplementary file 2: **Table S2.** Adverse events reporting in the included studies.

Figure 1
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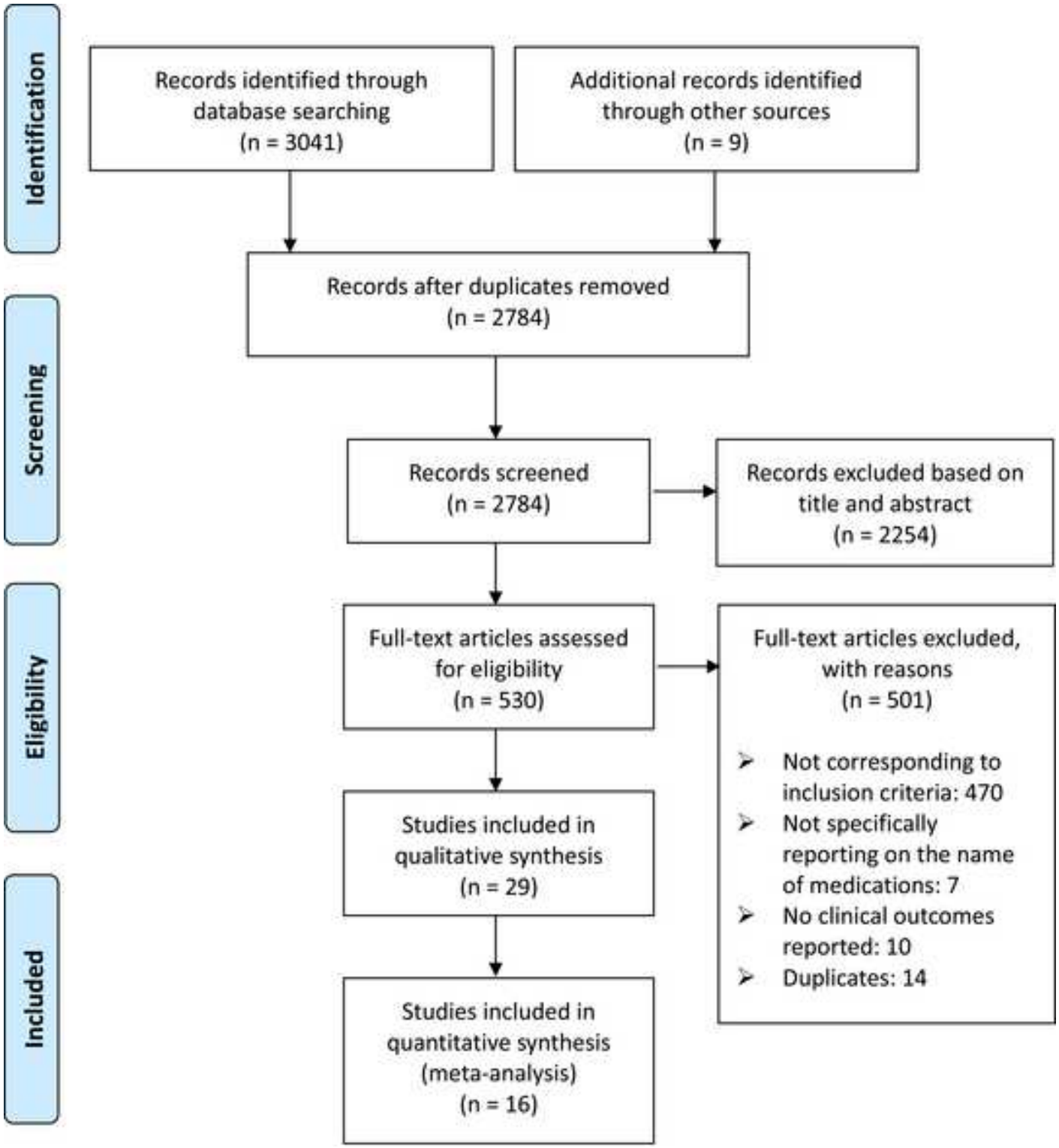

Figure 2

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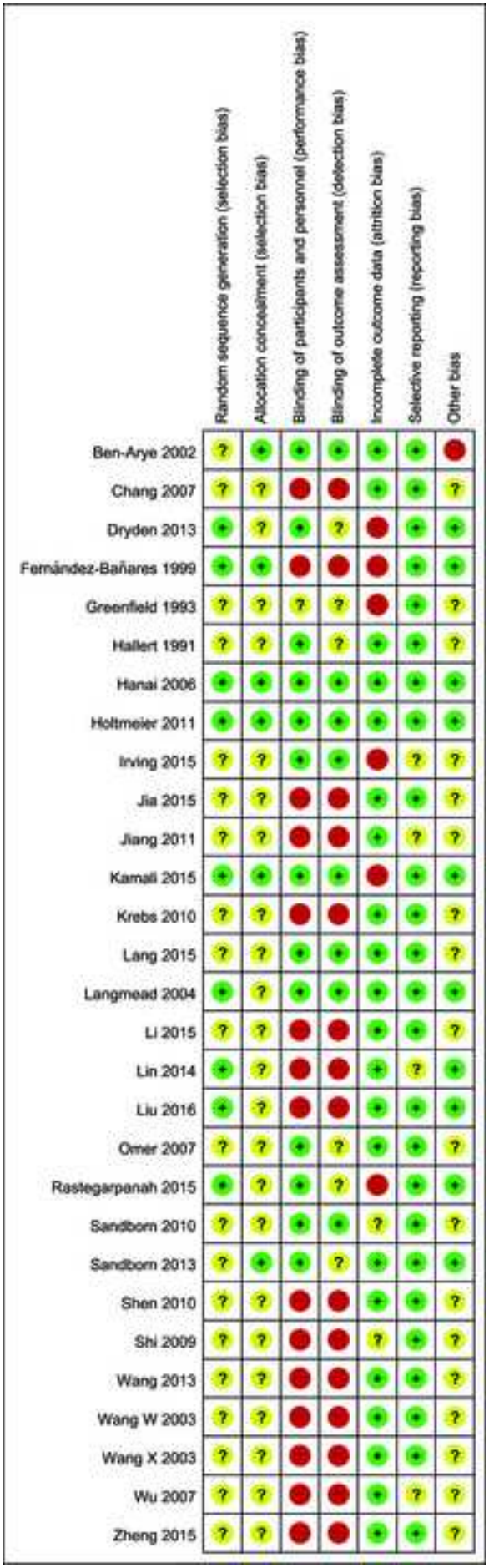

Figure 3

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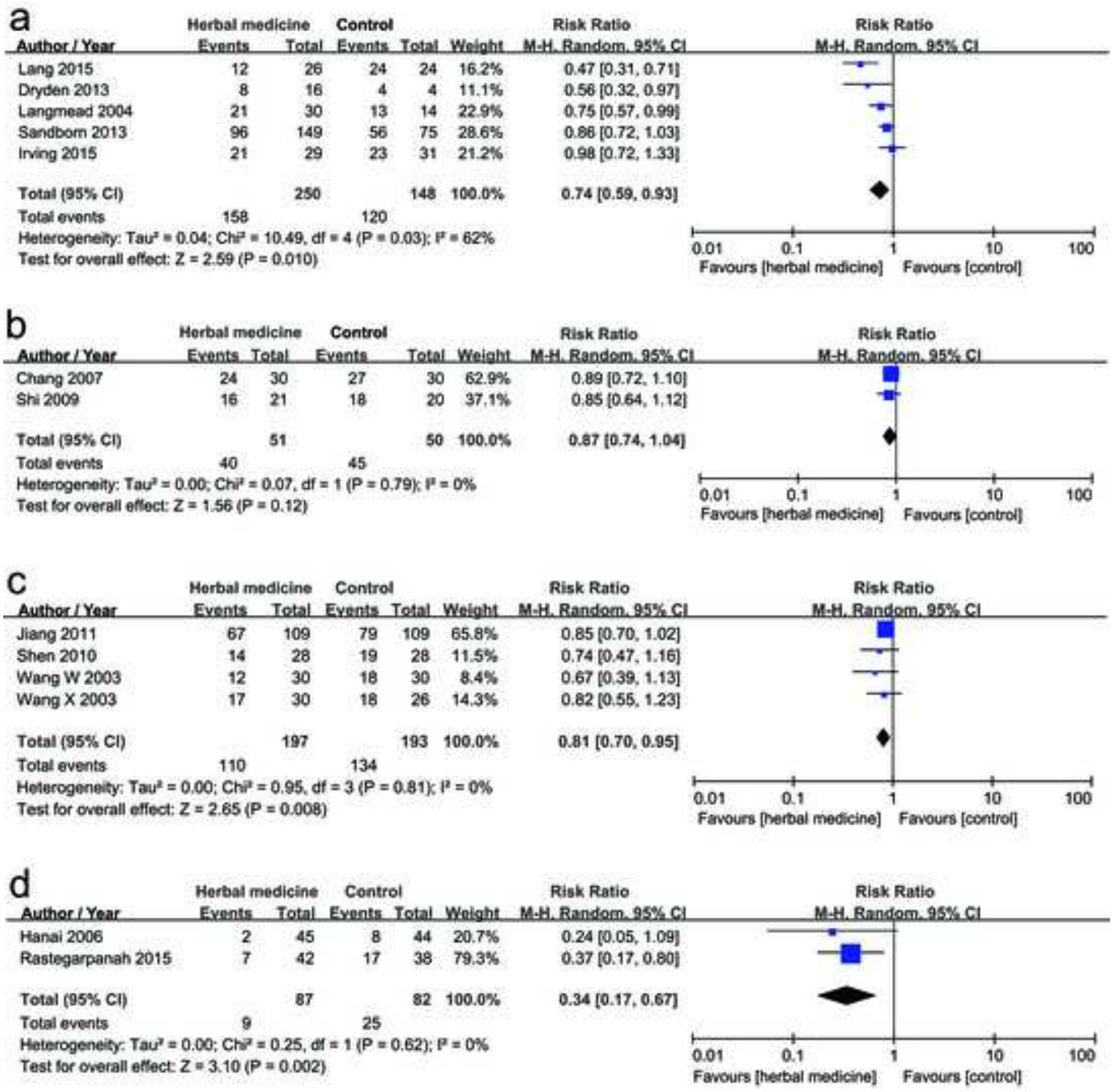

Figure 4

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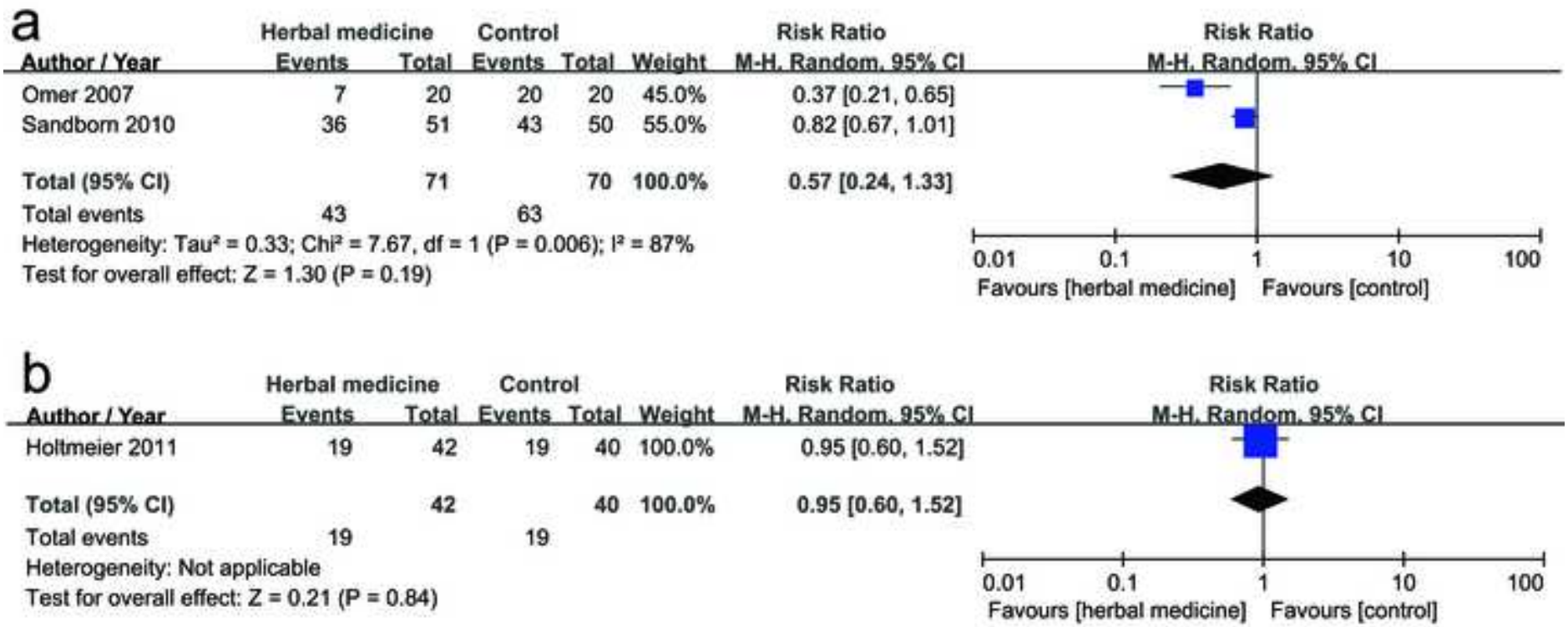

Table S1

Table S1. Supporting information for risk of bias assessment

Author (year)	Bias	Authors' judgement	Support for judgement
UC			
Kamali (2015)[1]	Random sequence generation (selection bias)	Low risk	Quote "Randomization was done using computer generated random numbers"
	Allocation concealment (selection bias)	Low risk	Quote "The *P.granatum* and placebo syrup were packed and alphabetically labeled in the same opaque and sealed bottles"
	Blinding of participants and personnel (performance bias)	Low risk	Quote "Attending physician, patients, principal investigators, and data analyzer were blinded to the study arms"
	Blinding of outcome assessment (detection bias)	Low risk	Quote "A co-investigator who was not involved in patients' recruitment or allocation or in outcome assessment was aware of the drug codes and cleared it after data analysis"
	Incomplete outcome data (attrition bias)	High risk	Per-protocol analysis was performed instead of intention-to-treat analysis
	Selective reporting (reporting bias)	Low risk	All stated outcomes were reported completely.
	Other bias	Low risk	Nothing special
Rastegarpanah (2015)[2]	Random sequence generation (selection bias)	Low risk	The study used a random number table.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Low risk	The study used a placebo control.
	Blinding of outcome assessment (detection bias)	Unclear risk	There is no description on the blinding of outcome assessment.
	Incomplete outcome data (attrition bias)	High risk	The study described that data were analyzed by using ITT approach, but the actual results did not include all patients' data.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing particular.
Lang (2015)[3]	Random sequence generation (selection bias)	Unclear risk	"On study entry, all patients were instructed to continue their optimized mesalamine medications unchanged and were randomly assigned in a 1:1 ratio… Sequential one-by-one blinded randomization was performed after stratification…"

			It is not clear how the random sequence was generated.
	Allocation concealment (selection bias)	Unclear risk	"All participating physicians were blinded to treatment assignment throughout the study except the clinician in charge of randomization, who did not participate in any assessment of the patients." However, there is no clear description on allocation concealment method.
	Blinding of participants and personnel (performance bias)	Low risk	Curcumin (Cur-Cure, a 95% pure curcumin preparation) and identical placebo capsules were both purchased from Bara Herbs Inc. (Yokneam, Israel).
	Blinding of outcome assessment (detection bias)	Low risk	The primary end point was the percentage of patients in clinical remission at the end of the 1-month treatment, defined as SCCAI score ≤ 2. (Participants were blinded and they were outcome assessors.)
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Irving (2015)[4]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Low risk	The study used a placebo control.
	Blinding of outcome assessment (detection bias)	Low risk	The study used Mayo score, which consists of objective outcome (e.g., stool frequency, rectal bleeding and findings of proctosigmoidoscopy) and subjective outcome assessed by physician who was blinded in this study.
	Incomplete outcome data (attrition bias)	High risk	Per-protocol analysis was performed instead of intention-to-treat analysis.
	Selective reporting (reporting bias)	Unclear risk	Because the study was not published as a form of full-text article, only primary outcome was reported in the text.
	Other bias	Unclear risk	Because the study was not published as a form of full-text article, only partial information was reported.
Dryden (2013)[5]	Random sequence generation (selection bias)	Low risk	Quote "Patients....were randomized in a double-blinded fashion according to a random number generator...."
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and	Low risk	The study used a placebo control.

	personnel (performance bias)		
	Blinding of outcome assessment (detection bias)	Unclear risk	There is no description of the blinding of outcome assessment.
	Incomplete outcome data (attrition bias)	High risk	Not all subjects were included in the analysis
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing special
Sandborn (2013)[6]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Low risk	Randomization was performed centrally...
	Blinding of participants and personnel (performance bias)	Low risk	A placebo control was used.
	Blinding of outcome assessment (detection bias)	Unclear risk	“Clinical response defined as a decrease from baseline in the total Mayo Score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute subscore of 0 or 1 point at 2 months. ... The primary efficacy end point was clinical response at week 8.” (Participants were blinded but it is not clear whether assessing physicians were also blinded.)
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing particular.
Hanai (2006)[7]	Random sequence generation (selection bias)	Low risk	The allocation was done by using a computer-generated randomization scheme.
	Allocation concealment (selection bias)	Low risk	The allocation was done by the clinical pharmacist.
	Blinding of participants and personnel (performance bias)	Low risk	"All study personnel and participants were blinded to treatment assignment for the duration of the study.”
	Blinding of outcome assessment (detection bias)	Low risk	"All study personnel and participants were blinded to treatment assignment for the duration of the study. Only the study statisticians and the data monitoring committee could see unblinded data, but none had any contact with the study patients."
	Incomplete outcome data	Low risk	Analyses were based on an intention-to-treat basis.

	(attrition bias)		
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing particular.
Langmead (2004)[8]	Random sequence generation (selection bias)	Low risk	"Those meeting the inclusion criteria were randomized by a trial pharmacist at Barts and the London NHS Trust, using a computer-generated, block-design, randomization sequence..."
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Low risk	The placebo consisted of a liquid preparation containing flavourings, but no known active agents (synthesized by Flavex International Ltd, Hereford, UK), which was identical in taste and appearance to the aloe vera preparation.
	Blinding of outcome assessment (detection bias)	Low risk	Blinded participants were outcome assessors. All histological grades were assessed by the same experienced histopathologist (RMF) blind to the treatment given.
	Incomplete outcome data (attrition bias)	Low risk	Although dropout and withdrawal rates were slightly high, all analysis was undertaken on an intention-to-treat basis using LOCF method.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing particular.
Ben-Arye (2002)[9]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Low risk	Centralized randomization process.
	Blinding of participants and personnel (performance bias)	Low risk	Matching placebo control was used. "...The placebo juice was manufactured from 0.18% normal saline with a mixture of under 0.5% weight kaolin and tragacanth, and tinted with food color (Fast Green FCF). The placebo juice was prepared in a centralized location and distributed monthly to the study coordinating centers. The placebo juice was similar to wheat grass juice in appearance, but not in taste and smell."
	Blinding of outcome assessment (detection bias)	Low risk	A disease activity index (DAI) was created by combining the four most accepted measures (according to Sutherland (7)): stool frequency, rectal bleeding, sigmoidoscopic score and physician's assessment of disease activity: gastroenterologists were blinded.
	Incomplete outcome data (attrition bias)	Low risk	Although the analyses were confined to the 21 patients who completed the trial, the dropout rates were not deemed to affect the outcomes.

	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	High risk	The numbers in the result table are not consistent.
Greenfield (1993)[10]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Unclear risk	The placebo used in the study was not identical to verum in terms of weight.
	Blinding of outcome assessment (detection bias)	Unclear risk	The participants reported the stool frequency on patient diary cards but it is not clear whether they were blinded or not.
	Incomplete outcome data (attrition bias)	High risk	The study did not include all patients' data in the analysis and this might have affected the outcomes.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Hallert (1991)[11]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Low risk	The study used a placebo control.
	Blinding of outcome assessment (detection bias)	Unclear risk	There is no description of the blinding of outcome assessment.
	Incomplete outcome data (attrition bias)	Low risk	Although the analyses were confined to the 29 patients who completed the trial, the dropout rates were not deemed to affect the outcomes.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no detailed description on randomisation method.
Liu (2016)[12]	Random sequence generation (selection bias)	Low risk	Random number table was used.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and	High risk	Herbal medicine was tested as an add-on to conventional medication.

	personnel (performance bias)		
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals and dropouts.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing particular.
Jia (2015)[13]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals and dropouts.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Li (2015)[14]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals and dropouts.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.

Lin (2014)[15]	Random sequence generation (selection bias)	Low risk	Random number table was used.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Unclear risk	Endoscopic results were reported without pre-defined criteria for grading.
	Other bias	Low risk	Nothing particular.
Wang (2013)[16]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Low risk	Important outcome of interest, i.e. remission, was reported.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Jiang (2011)[17]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data	Low risk	There were no withdrawals and dropouts.

	(attrition bias)		
	Selective reporting (reporting bias)	Unclear risk	Symptoms and endoscopic evaluations were reported without a reference, i.e. pre-defined or validated criteria for grading.
	Other bias	Unclear risk	This may not be a truly randomised trial because there were no descriptions on randomisation method, and dropouts and withdrawals.
Shen (2010)[18]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Low risk	Important outcome of interest, i.e. remission, was reported.
	Other bias	Unclear risk	This may not be a truly randomised trial because there were no descriptions on randomisation method.
Shi (2009)[19]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Unclear risk	There was no description on withdrawals and dropouts and the analyses were based on the participants who completed the trial.
	Selective reporting (reporting bias)	Low risk	Important outcome of interest, i.e. remission, was reported.
	Other bias	Unclear risk	This may not be a truly randomised trial because there were no descriptions on randomisation method, and dropouts and withdrawals.
Chang (2007)[20]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment	Unclear risk	No description of allocation concealment.

	(selection bias)		
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	There were no dropouts and withdrawals.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there were no descriptions on randomisation method, and dropouts and withdrawals.
Wu (2007)[21]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Unclear risk	Symptoms and endoscopic evaluations were reported without a reference, i.e. pre-defined or validated criteria for grading.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Wang W (2003)[22]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting	Low risk	All planned outcomes were reported in detail.

	bias)		
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Wang X (2003)[23]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	Analyses were based on an intention-to-treat basis.
	Selective reporting (reporting bias)	Unclear risk	Symptoms and endoscopic evaluations were reported without a reference, i.e. pre-defined or validated criteria for grading.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Fernández-Bañares (1999)[24]	Random sequence generation (selection bias)	Low risk	Allocation sequence was computer-generated.
	Allocation concealment (selection bias)	Low risk	"The randomization was governed by a centrally held code to ensure an equal and random allocation at each center."
	Blinding of participants and personnel (performance bias)	High risk	The study was an open-label trial. (Herbal medicine was tested as an add-on to conventional medication.)
	Blinding of outcome assessment (detection bias)	High risk	Patients who were not blinded wrote a daily symptom diary.
	Incomplete outcome data (attrition bias)	High risk	Not all patients were included in analysis.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Low risk	Nothing particular.
CD			
Zheng (2015)[25]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.

	Blinding of participants and personnel (performance bias)	High risk	Herbal medicine was tested as an add-on to conventional medication.
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals and dropouts.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Holtmeier (2011)[26]	Random sequence generation (selection bias)	Low risk	"Eighty two patients were randomized according to a computer-generated randomization scheme."
	Allocation concealment (selection bias)	Low risk	"Due to a low patient recruitment rate and a comparatively high dropout rate we decided to perform an unscheduled interim analysis with known treatment strata A and B, but unknown allocation of drug and placebo to A and B. ... Medication was dispensed to each center in coded identical-appearing boxes."
	Blinding of participants and personnel (performance bias)	Low risk	"The placebo was the same soft gelatin capsule containing propylene glycol monolaurate and the excipients only. ... Blinding was done by providing placebo capsules that were of identical appearance (size, colour, weight, taste) in comparison to verum."
	Blinding of outcome assessment (detection bias)	Low risk	The participants were blinded outcome assessors.
	Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat and per-protocol analyses were done and compared.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail although the trial was stopped early.
	Other bias	Low risk	Nothing particular.
Sandborn (2010)[27]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Low risk	The study used a placebo control.
	Blinding of outcome assessment (detection bias)	Low risk	The outcome was assessed by using CDAI, which consists of objective outcomes (e.g., number of liquid or soft stools and hematocrit) and subjective outcomes (e.g., abdominal pain and general wellbeing) assessed by patients who were

			blinded.
	Incomplete outcome data (attrition bias)	Unclear risk	No description of dropout rate.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	Because the study was not published as a form of full-text article, only partial information was reported.
Krebs (2010)[28]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	High risk	This study was an open-label trial. (Herbal medicine was tested as an add-on to conventional medication.)
	Blinding of outcome assessment (detection bias)	High risk	Symptoms and endoscopic results were assessed by participants and physicians who are (probably) unblinded.
	Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals and dropouts.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.
Omer (2007)[29]	Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
	Blinding of participants and personnel (performance bias)	Low risk	The study used a placebo control.
	Blinding of outcome assessment (detection bias)	Unclear risk	There is no description of the blinding of outcome assessment.
	Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals and dropouts.
	Selective reporting (reporting bias)	Low risk	All planned outcomes were reported in detail.
	Other bias	Unclear risk	This may not be a truly randomised trial because there was no description on randomisation method.

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Table S2. Adverse events reporting in the included studies.

Author (year)	Herbal medicine	Duration of therapy (months)	No. of patients allocated to intervention group	No. of AEs occurring in the intervention group	No. of patients allocated to control group	No. of AEs occurring in the control group
UC						
Liu (2016)[1]	Gu chang zhi xie wan	1.5	70	Gastric discomfort (2) Nausea (1) Others (2)	70	Gastric discomfort (6) Nausea (4) Others (3)
Kamali (2015)[2]	*Punica granatum* peel aqueous extract syrup	1	39	Urticaria (2) Nausea (2) Increased appetite (2)	39	Urticaria (2) Nausea (1) Increased appetite (3)
Jia (2015)[3]	Kui jie ling granule	3	80	Diarrhoea (2) Abdominal pain (1) Bloating (1) Mucous stool (1) Bloody stool (1) Tenesmus (0) Abnormal liver function test results (2)	80	Diarrhoea (3) Abdominal pain (3) Bloating (2) Mucous stool (3) Bloody stool (2) Tenesmus (2) Abnormal liver function test results (4)
Lang (2015)[4]	Curcumin capsules	1	26	Worsening symptoms necessitating early termination and the initiation of corticosteroids (1)	24	Worsening symptoms necessitating early termination and the initiation of corticosteroids (1)
Li (2015)[5]	Chang yu ning granule	2	21	Gastric discomfort, light abdominal pain (2)	20	Gastric discomfort (2)
Rastegarpanah (2015)[6]	Silymarin (Silybummarianum seed extract) tablets	6	42	Headache (8) Rash (2) Diarrhoea (6) Abdominal pain (5) Nausea (4)	38	Headache (4) Rash (1) Diarrhoea (3) Abdominal pain (6) Nausea (1)
Irving (2015)[7]	GWP42003 (hard gelatin capsule containing cannabidiol and Δ^9-	2.5	29	NR	31	NR

	tetrahydrocannabinol extracted from *Cannabis sativa* L.)					
Dryden (2013)[8]	Polyphenon E capsules containing (-)-epigallocatechin-3-gallate (EGCG)	2	16	Hospitalisation triggered by antibiotics administered for sinusitis (1) Heartburn (4) Bloating, flatulence (4) Nausea (3) Headache (2) Increased thirst (1) Increased diarrhoea (1)	4	Bloating, flatulence (1) Nausea (1) Headache (1)
Sandborn (2013)[9]	HMPL-004 (*Andrographis paniculata* ethanol extract)	2	149 (75 to 1,200 mg group and 74 to 1,800 mg group)	Any AEs including the ones leading to study drug discontinuation and serious ones (45 for 1,200 mg group and 39 for 1,800 mg group)	75	Any AEs including the ones leading to study drug discontinuation and serious ones (45)
Hanai (2006)[10]	Curcumin	6	45	Abdominal bulging, nausea, transient hypertension, transient increase in the number of stools, and elevated γ-guanosine triphosphate level (9)	44	NR
Langmead (2004)[11]	Aloe vera gel	1	30	Withdrawals due to deterioration or a failure to improve sufficiently (6) Abdominal bloating (1) Pain in the feet (1) Sore throat (1) Transient ankle swelling (1) Acne (1) Eczema worsening (1)	14	Withdrawals due to deterioration or a failure to improve sufficiently (3) Bloating (2) Pain in the feet (1) Acne (1)
Ben-Arye (2002)[12]	Wheat grass juice	1	11	Nausea (4) Decreased morning appetite (2) Constipation (1) Increased vitality (5)	12	Deterioration in illness (1)
Greenfield (1993)[13]	Evening primrose oil	6	19	NR	8	NR

Lin (2014)[14]	Chang yu ning granule	1	30	No AEs	30	No AEs
Wang (2013)[15]	Chang yu ning granule	1	30	No AEs	30	Headache (5) Nausea and vomiting (3)
Jiang (2011)[16]	Bu pi yi chang pill	2	109	NR	109	NR
Shen (2010)[17]	Bu pi yi chang pill	3	28	NR	28	NR
Shi (2009)[18]	Chang yu ning granule	2	22	Gastrointestinal discomfort and lack of strength (3)	22	Nausea, anorexia, and headache (6)
Chang (2007)[19]	Kui jie ling granule	12	30	NR	30	NR
Wu (2007)[20]	Chang yan ning syrup	2	48	Gastrointestinal discomfort, rash, dizziness, abnormal liver function, and leukopenia (7)	44	Gastrointestinal discomfort, rash, dizziness, abnormal liver function, and leukopenia (7)
Wang W (2003)[21]	Bu pi yi chang pill	1	30	Nausea, vomiting, abdominal distension, and gastrointestinal discomfort (1) Rash (2)	30	Nausea, vomiting, abdominal distension, and gastrointestinal discomfort (13) Rash (2)
Wang X (2003)[22]	Yunnan Bai yao capsule	1	30	NR	26	NR
Fernández-Bañares(1999)[23]	*Plantago ovate* (PO) seeds	12	31	Total number of AEs (9)	38	Total number of AEs (5)
Hallert (1991)[24]	Vi-Siblin® S granules (containing 3.52 g of Ispaghula husk)	2	36	Relapse of colitis (1)	36	Relapse of colitis (3) Abdominal pain (1)
CD						
Zheng (2015)[25]	Shen ling bai zhu wan	2	40	Nausea and vomiting (3) Aphthous stomatitis (1) Hair loss (1) Abnormal liver function test results (0) Abnormal blood test results (0) Exanthemata (1)	40	Nausea and vomiting (4) Aphthous stomatitis (2) Hair loss (1) Abnormal LFT results (0) Abnormal blood test results (0) Exanthemata (0)

Holtmeier (2011)[26]	Boswelan (*Boswellia serrata* resin extract) capsules	12	42	Total number of AEs (59)	40	Total number of AEs (69)
Krebs (2010)[27]	SedaCrohn® (*Artemisia absinthium* powder) capsules	1.5	10	No AEs	10	NR
Sandborn (2010)[28]	HMPL-004 (*Andrographis paniculata* ethanol extract)	2	51	Total number of AEs, i.e., skin rash, slight increase in bronchitis and urinary tract infections (33) Serious AEs: CD exacerbation (2)	50	Total number of AEs (28) Serious AEs: CD exacerbation (3); development of lung cancer (1)
Omer (2007)[29]	SedaCrohn® (*Artemisia absinthium* powder) capsules	2.5	20	NR	20	NR

AEs, Adverse events; CD, Crohn's disease; NR, not reported; UC, ulcerative colitis.

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