Journal of Crohn's and Colitis, 2015, 86–106
doi:10.1093/ecco-jcc/jju007
Advance Access publication December 4, 2014
Review Paper

Review Paper

Systematic Review of Complementary and Alternative Medicine Treatments in Inflammatory Bowel Diseases

J. Langhorst,[a,b] H. Wulfert,[b] R. Lauche,[b,c] P. Klose,[b] H. Cramer,[b,c] G.J. Dobos,[b] J. Korzenik[d]

[a]Department of Integrative Gastroenterology, Faculty of Medicine, University of Duisburg-Essen, Germany
[b]Department of Internal and Integrative Medicine, Faculty of Medicine, University of Duisburg-Essen, Germany
[c]Australian Research Centre in Complementary and Integrative Medicine[], Faculty of Health, University of Technology Sydney, Australia [d]Department of Inflammatory Bowel Disease, Harvard Medical School, Boston, MA, USA

Corresponding author: Jost Langhorst, MD, Integrative Gastroenterology, Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Am Deimelsberg 34a, D-45276 Essen, Germany. Tel: +49 201 174 25001; Fax: +49 201 174 25000; Email: jost.langhorst@gmx.de

Abstract

Objective: We performed a systematic review for Complementary and Alternative Medicine [CAM] as defined by the National Institute of Health in Inflammatory Bowel Disease [IBD], ie Crohn's disease [CD] and ulcerative colitis [UC], with the exception of dietary and nutritional supplements, and manipulative therapies.

Methods: A computerized search of databases [Cochrane Library, Pubmed/Medline, PsychINFO, and Scopus] through March 2014 was performed. We screened the reference sections of original studies and systematic reviews in English language for CAM in IBD, CD and UC. Randomized controlled trials [RCT] and controlled trials [CT] were referred and assessed using the Cochrane risk of bias tool.

Results: A total of: 26 RCT and 3 CT for herbal medicine, eg aloe-vera gel, andrographis paniculata, artemisia absinthium, barley foodstuff, boswellia serrata, cannabis, curcumin, evening primrose oil, Myrrhinil intest®, plantago ovata, silymarin, sophora, tormentil, wheatgrass-juice and wormwood; 1 RCT for trichuris suis ovata; 7 RCT for mind/body interventions such as lifestyle modification, hypnotherapy, relaxation training and mindfulness; and 2 RCT in acupuncture; were found. Risk of bias was quite heterogeneous. Best evidence was found for herbal therapy, ie plantago ovata and curcumin in UC maintenance therapy, wormwood in CD, mind/body therapy and self-intervention in UC, and acupuncture in UC and CD.

Conclusions: Complementary and alternative therapies might be effective for the treatment of inflammatory bowel diseases; however, given the low number of trials and the heterogeneous methodological quality of trials, further in-depth research is necessary.

Keywords: Ulcerative colitis, Crohn's disease, CAM, complementary and alternative medicine, review

1. Introduction

Patients with inflammatory bowel disease [IBD] rank among the highest users of complementary and alternative medicines [CAM], with current or past use of CAM ranging from 21–60%.[1–9] Their primary motivations include an inadequate response to available medications or concerns over side effects.

The use of complementary and alternative medicine [CAM] is widespread in Western Europe and North America,[10,11] particularly by those individuals with chronic diseases.[12–15] The National Center for Complementary and Alternative Medicine defines CAM as a group of diverse medical systems, practises and products that are not presently considered to be part of conventional medicine.[16] The term 'alternative medicine', furthermore, implies that this is used instead of, and the term 'complementary medicine' that this is used integrated with, conventional medicine. As we demonstrated in our previous work, only 48.1% of IBD patients regarded a scientific foundation for CAM treatments as being important.[8] Indeed, a considerable number would use a CAM treatment even if research proved that it yields negative results, indicating that physicians' reasons for therapy differ from those of patients.[8]

Often commonly used approaches are supported by little or no valid scientific studies. Greater interest in CAM worldwide has led to increased scientific investigation in the field.[10,17] We performed a systematic review for Complementary and Alternative Medicine [CAM], as defined by the National Institute of Health in Inflammatory Bowel Disease [IBD;] i.e. Crohn´s disease [CD] and ulcerative colitis [UC], with the exception of dietary and nutritional supplements. The possibility of meta-analysis was considered separately for every field of CAM presented but could not be performed due to heterogeneous study designs and outcome measures. Inflammatory bowels diseases like Crohn´s disease and ulcerative colitis [UC] are chronic relapsing diseases. Though recent progress in research has deepened our understanding of the diseases, there is no cure to date. Chronic therapy for IBD is needed given the difficulty of predicting and controlling the frequency and severity of disease exacerbations. In addition, a significant proportion of patients are not sufficiently helped by conventional therapy or suffer from relevant adverse events. This paper aims to identify and review RCTs on CAM in IBD and offer both an overview of the field with tables, and a summary of the evidence in the different CAM categories.

2. Methods

2.1. Protocol and registration

This review was planned and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [PRISMA].[18] The protocol was not registered on any database.

2.2. Eligibility criteria

To be eligible for review, studies were required to meet the following conditions:

1] Types of study designs: controlled clinical trials, randomized controlled trials, randomized controlled cross-over trials, cluster randomized trials. Studies that investigated the effects of therapies within one group only [eg dosage-finding studies] were not considered eligible.

2] Types of participants: Studies of patients diagnosed with ulcerative colitis and/or Crohn's disease were eligible, regardless of age, condition's duration or the state [remission, active]. Studies were not included if IBS was not the targeted disease but was associated with the targeted disease. No restrictions regarding diagnostic procedures were applied.

3] Types of interventions: Studies that investigated CAM therapies according to the NIH definition[16] were eligible. These included natural products such as herbs, botanicals, or helminthes; mind/body interventions such as meditation, relaxation techniques, stress management except for psychotherapy, mindfulness-based stress reduction, comprehensive lifestyle modification programs, hypnosis, yoga, tai chi or qigong, fasting, traditional Chinese medicine interventions, ayurvedic, anthroposophic or homeopathic therapies, balneotherapy, acupuncture, acupressure and cataplasm. Massages and manipulative therapies were beyond the scope of this review and not included. Studies investigating probiotics or omega-3 fatty acids, fish oils, or essential oils as well as vitamins and minerals were also excluded.

4] Types of outcomes: Studies were eligible if they assessed at least one of the following outcomes: induction or maintenance of remission, disease activity or symptom severity, quality of life, or psychological variables. Safety would also be addressed.

5] Length of follow-up: No restrictions regarding length of follow-up were applied.

6] Accessibility of data: Studies were eligible only if they were published as full papers, and only English or German language publications were considered eligible.

2.3. Literature search

The following electronic databases were searched from their inception through to March 12, 2014: Pubmed/MEDLINE, Scopus, Cochrane central register of controlled trials and PsycInfo. The literature search, which was constructed around search terms for ulcerative colitis/Crohn's disease and CAM therapies, was adapted for each database as necessary. The complete search strategy used on the Pubmed/MEDLINE database is shown in Box 1.

The search was limited to articles in English and German and to studies with adult humans and was adapted for the other databases accordingly.

Two reviewers screened the abstracts of the candidate studies individually. The selected studies were then checked in detail on evaluation of the full manuscript, with eligible papers being included in the systematic review.

Two reviewers independently extracted data on studies' characteristics [participants, interventions, control conditions, co-interventions, outcome measures, results]. Disagreements were checked with a third reviewer and resolved by agreement.

The risk of bias at study level was assessed by two independent reviewers using the 2006 Method guidelines for systematic reviews of the Cochrane Musculoskeletal Group.[19] These guidelines recommend the imposition of seven quality criteria, each of which is rated as 'low risk', 'high risk', or 'unclear risk of bias'. These criteria relate to the following risk-of-bias categories: random sequence generation [selection bias], allocation concealment [selection bias], blinding of participants and personnel [performance bias], blinding of outcome assessors [detection bias], incomplete outcome data [attrition bias], selective reporting [reporting bias], and other bias relating to major study flaws.

If study data were inconclusive, trial authors were contacted for further study details. Studies that scored positive on at least 6 of the 12 criteria and had no serious flaw were rated as having low risk of bias. Studies that met fewer than 6 criteria or showed a serious flaw were rated as having high risk of bias.[19]

Box 1. Complete search strategy for Pubmed/Medline.

#1	'Inflammatory bowel diseases'[MeSH Terms] OR 'inflammatory bowel diseases'[Title/Abstract] OR 'colitis, ulcerative'[MeSH Terms] OR 'colitis, ulcerative'[Title/Abstract] OR 'crohn disease'[MeSH Terms] OR 'crohn disease'[Title/Abstract]
#2	'Complementary therapies'[MeSH Terms] OR 'complementary therapies'[Title/Abstract] OR 'alternative medicine'[Title/Abstract]
#3	Phytotherapy[Title/Abstract] OR herbal[Title/Abstract] OR valerian[Title/Abstract] OR belladonna[Title/Abstract] OR glycyrrhiza[Title/Abstract] OR calendula[Title/Abstract] OR 'plantago ovata' [Title/Abstract] OR ginger[Title/Abstract] OR turmeric[Title/Abstract] OR myrrh[Title/Abstract] OR tormentil[Title/Abstract] OR curcumin[Title/Abstract] OR caraway[Title/Abstract] OR frankincense[Title/Abstract] OR 'boswellia serrata'[Title/Abstract] OR 'wheat grass'[Title/Abstract] OR barley[Title/Abstract] OR 'aloe vera'[Title/Abstract] OR 'trichuris suis ova'[Title/Abstract] OR helminths[Title/Abstract]
#4	'Mind body'[Title/Abstract] OR 'Lifestyle modification'[Title/Abstract] OR 'Autogenic training'[Title/Abstract] OR MBSR[Title/Abstract] OR Meditation[Title/Abstract] OR Hypnosis[Title/Abstract] OR 'Qi gong'[Title/Abstract] OR 'Qi kung'[Title/Abstract] OR 'Tai chi'[Title/Abstract] OR 'Taiji'[Title/Abstract] OR 'T'ai chi'[Title/Abstract] OR Yoga[Title/Abstract] OR Fasting[Title/Abstract]
#5	TCM[Title/Abstract] OR 'Chinese medicine'[Title/Abstract] OR Ayurveda[Title/Abstract] OR Ayurvedic[Title/Abstract] OR Anthroposophy[Title/Abstract] OR Anthroposophic[Title/Abstract] OR Homeopathy[Title/Abstract] OR Homeopathic[Title/Abstract] OR balneotherapy[Title/Abstract] OR acupuncture[Title/Abstract] OR acupressure[Title/Abstract] OR moxibustion[Title/Abstract] OR cataplasm[Title/Abstract]
#6	Randomized controlled trial[PT] OR controlled clinical trial[PT] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]
#7	#2 OR #3 OR #4 OR #5
#8	#1 AND #6 AND #7
#9	Animals[MeSH Terms] NOT humans[MeSH Terms]
#10	#8 NOT #9

3. Results

3.1. Literature search

The literature search [Figure 1] yielded a total of 1729 papers, with 263 duplicates, leaving 1466 hits for abstract screening. After abstract screening, 35 studies were considered potentially eligible and read in full text. After exclusion of another 6 full-text articles,[20–25] 29 full-text articles were included in the systematic review.[26–54]

Of those, 29 studies were identified for this review; 26 of them were RCTs, and 3 were non-randomized lled trials. Trials were categorized in distinct groups: herbs and botanicals [*n* = 19]; mind/body medicine [*n* = 7]; acupuncture [*n* = 2], and trichuris suis ova [*n* = 1]. The targeted diseases included ulcerative colitis [*n* = 20], Crohn's disease [*n* = 6] or inflammatory bowel disease [both UC or CD] [*n* = 3]. The study sizes ranged from 22 to 224 patients, allocated to 2 or 3 groups respectively. Studies details are presented in Table 1.

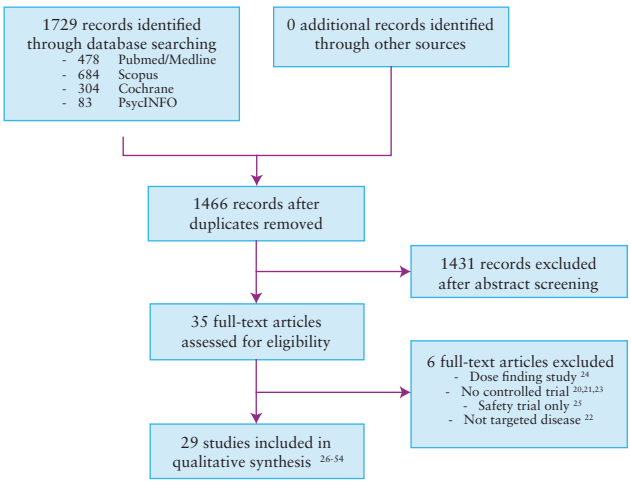

Figure 1. Flowchart of the results of the literature search.

The risk of bias [Table 2] was quite heterogeneous, from studies with a high risk in almost all domains to studies with no apparent risk of bias in any domain. The most critical domains for risk of bias were random sequence generation and allocation concealment, with one-third of the studies not reporting adequate methods. Data on compliance were not provided in almost half of the trials. Blinding of participants, providers, and outcome assessors was satisfactory in trials on herbal medicine, but not feasible in trials on behavioral interventions. Finally, although the drop-out rate in many trials was acceptable, only the minority of trials analyzed primary results in an intention-to-treat analysis.

3.1.1. Herbs and botanicals

Nineteen studies were identified evaluating herbs and botanicals in IBD, including studies on: boswellia serrata [*n* = 4]; artemisia absinthium [*n* = 2]; andrographis paniculata [*n* = 2]; and curcumin [*n* = 2]; and 1study each on aloe vera, cannabis, germinated barley, Myrrhinil intest®, plantago ovata, silymarin, sophora, super evening primrose, and wheat grass juice [Table 1].

3.1.2. Boswellia serrata [Indian frankincense]

Two randomized[30,36] and two non-randomized controlled trials[32,33] were available for boswellia serrata. They were tested in patients with ulcerative colitis[32,33] or Crohn's disease,[30,36] for active disease[30,32,33] or maintenance of remission.[36]

Gerhard et al.[30] investigated 102 patients who received either boswellia serrata or mesalazine in a double blind manner for 8 weeks. At Week 8 there was no significant difference regarding disease activity or remission rates, and furthermore no serious adverse events had been observed.

Gupta et al.[32,33] tested the efficacy of different doses of boswellia serrata compared with sulfasalazine in two non-randomized studies; 42[33] and 30[32] patients with ulcerative colitis, respectively, received treatment for 6 weeks. The tested outcomes included remission, severity of IBD symptoms, and safety. None of the tested variables revealed any significant difference between the groups; adverse events included nausea, epigastric pain, heartburn and a lack of appetite, and were present in 6 of 42 and 2 of 30 patients, respectively.

Table 1. Characteristics of included trials sorted by type of interventions.

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
HERBS AND BOTANICALS: Boswellia serrata								
Gerhard, 2001	Active CD	102, 2 groups; [50 BS; 52 ME]	RCT Double-blinded Verum-controlled	Boswellia-serrata-extract H15 [BS]; 3, 6 g daily for 8 weeks	Mesalazine [ME]; 4,5 g daily for 8 weeks	2, 4, 6, 8 weeks	1. CDAI 2. Remission 3. Adverse events	1, 2. n.s. 3. 8 patients in BS, 15 patients in ME; no serious adverse events
Gupta, 1997	UC	42, 2 groups [34 BS, 8 SU]	Non-randomized Verum-controlled Open-label	Boswellia serrata gum resin [BS]; 3 x 350 mg daily for 6 weeks	Sulfasalazine [SU]; 3 x 1 g daily for 6 weeks	6 weeks	1. Remission 2. Abdominal pain 3. Sigmoidoscopic examination 4. Rectal biopsy 5. Stool sample 6. Grading of colitis 7. Body weight 8. Laboratory testing: Hb, iron, phosphorus,calcium, protein, leukocytes, eosinophils 9. Adverse events	1, 2, 3, 4, 5, 6, 7, 8. n.s. 9. 6 patients in BS; no serious adverse events
Gupta, 2001	UC	30, 2 groups; [20 BS, 10 SU]	Non-randomized Verum-controlled Open-label	Boswellia serrata gum resin [BS]; 3 x 300mg daily for 6 weeks	Sulfasalazine [SU]; 3 x 1g daily for 6 weeks	6 weeks	1. Remission 2. Abdominal pain 3. Sigmoidoscopic examination 4. Rectal biopsy 5. Stool sample 6. Grading of colitis 7. Body weight 8. Laboratory testing: Hb, iron, phosphorus,calcium, protein, leukocytes, eosinophils 9. Adverse events	1, 2, 3, 4, 5, 6, 7, 8. n.s. 9. 2 patients in BS; no serious adverse events
Holtmeier, 2010	CD in clinical remission	82, 2 groups [42 BS, 40 Placebo]	RCT Placebo-controlled Double-blinded	Boswellia serrata extract PS0201Bo [BS]; 6 x 400 mg daily for 12 months	Placebo; For 12 months	4, 16, 28, 40, 52, 64 weeks	1. Maintenance of remission 2. Time to relapse 3. CDAI 4. IBDQ 5. Adverse events	1. n. s. 2. n. s. 3. n. s. 4. n. s. 5. 29 patients in BS, 34 patients in Placebo; no serious adverse events

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
HERBS AND BOTANICALS: Artemisia absinthium								
Krebs, 2010	CD	20, 2 groups [10 AA, 10 ST]	RCT Standard-carecontrolled Open-label	Artemisia absinthium [AA]; 9 x 250mg daily in addition to standard treatment	Standard treatment [ST]	3, 6 weeks	1. TNF- α 2. Clinical improvement [CDAI] 3. IBDQ 4. Hamilton depression scale [HAMD]	1. Sig. decrease in AA compared with ST at 6 weeks 2. Sig. decrease in CDAI in AA but not ST 3. Sig. increase in AA but not ST 4. Sig. decrease in AA but not ST Sig. group differences in favor of AA
Omer	CD	40, 2 groups [20 AA, 20 Placebo]	RCT Placebo-controlled Double-blinded	Artemisia absinthium [AA]; 6 x 250mg daily for 10 weeks; in addition to steroid or prednisolone [constant dose until Week 2, gradually reduced dose until free of steroids in Week 10]	Placebo; in addition to steroid or prednisolone [constant dose until Week 2, gradually reduced dose until free of steroids in Week 10]	2, 4, 6, 8, 10, 12, 16, 20	1. CDAI 2. IBDQ 3. HAMD 4. Subjective well-being [VAS]	1. Sig. decrease in CDAI in AA after Weeks 6, 8, 20 compared with Placebo 2, 3. n.s. 4. Sig. increase in VAS in AA after 8, 10, 12 weeks compared with Placebo
HERBS AND BOTANICALS: Andrographis paniculata								
Sandborn, 2013	Active UC	224, 3 groups [75 HMPL1, 74 HMPL2, 75 Placebo]	RCT placebo-controlled double-blinded	Andrographis paniculata extract [HMPL-004] HMPL1: 1200 mg HMPL2: 1800 mg 3 doses daily for 8 weeks + stable dose of mesalamine	Placebo + stable dose of mesalamine	8 weeks	1. Clinical response 2. Clinical remission 3. Mucosal healing 4. MAYO score 5. Safety	1. Sig. group difference in favor of HMPL 2. n.s. 3. n.s. 4. n.s. 5. 8% of patients in HMPL: similar, except for mild rashes, 2 adverse events in each group

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
Tang, 2011	Active UC	120, 2 groups [60 AP, 60 ME]	RCT Controlled? Double-blinded	Andrographis paniculata, HMPL-2004 [AP]; 3 x 400mg daily for 8 weeks	Mesalazine [ME]; 3 x 1500mg daily for 8 weeks	2, 4, 6, 8 weeks	1. Clinical efficacy [DAI] 2. Endoscopic efficacy [EI] 3. Histologic efficacy	1. Sig. overall efficacy in AP and ME after 8 weeks compared with baseline 2. Sig. overall efficacy in AP and ME after 8 weeks compared with baseline 3. Sig. improvement in AP and ME after 8 weeks compared with baseline
HERBS AND BOTANICALS: Curcumin								
Hanai, 2006	Quiescent UC	89, 2 groups [45 CU, 44 Placebo]	RCT Placebo-controlled Double-blinded	Curcumin [CU]; 2 g daily for 6 months; in addition to Sulfasalazine, 1 3 g, or Mesalamine, 1.53 g	Placebo in addition to Sulfasalazine, 1 3 g, or Mesalamine, 1.53 g, for 6 months	2, 4, 6, 12 months	1. CAI 2. Endoscopic index 3. Recurrence rate 4. Adverse events	1, 2, 3. Sig. lower in CU compared with Placebo at 6 months 4. 7 patients; no serious adverse events
Singla, 2014	Mild-to-moderate active UC	43, 2 groups [23 curcuma, 22 Placebo]	RCT Placebo-controlled Double-blinded	NCB-02 [curcuma longa; 72% curcumin, 18% demethoxy curcumin, 9% bis-demethoxy curcumin] enema [140 mg in 20 ml of water] once daily for 8 weeks + 800 mg oral mesalamine twice daily	Placebo enema enema [140 mg in 20 ml of water] once daily for 8 weeks + 800 mg oral mesalamine twice daily	8 weeks	1. Disease activity [UCDAI] 2. Remission rate [UCDAI <3] 3. Endoscopic disease activity 4. Adverse events	1. n.s. 2. n.s. 3. n.s. 4. n.s.

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
HERBS AND BOTANICALS: Others								
Ben-Arye, 2002	Active distal UC	24, 2 groups; [12 WG; 12 Placebo]	RCT Placebo-controlled Double-blinded	Wheat Grass Juice [WG]; 100 ml daily for 4 weeks [starting with 20 ml and increasing the dose by 20 ml each day until 100 ml]	Placebo; 100 ml daily for 4 weeks [starting with 20 ml and increasing the dose by 2 0ml each day until 100 ml]	4 weeks	1. DAI score 2. Rectal bleeding 3. Stool frequency 4. Sigmoidoscopic score 5. PGA [Physician global assessment] 6. Patients' retrospective evaluation 7. Mucus 8. Abdominal pain 9. Abdominal bloating 10. Number of bowel movements 11. Adverse events	1, 2, 5, 6, 8. Sig. differences in favor of WG 3, 4, 7, 9, 10. n.s. 11. No serious adverse events
Fernandez-Banares, 1999	UC in remission	102, 3 groups; [35 PO; 37 ME; 30 PO + ME]	RCT Verum-controlled Open-label	Plantago ovata seeds [PO]; 20 g daily for up to 12 months	Mesalamine [ME]; 1.5 g daily Plantago ovata + Mesalamine [PO + ME]	3, 6, 9, 12 months	1. Maintenance of remission 2. SCFA production [short-chain fatty acid] 3. Adverse events	1. n.s. after 12 months 2. Sig. increase in butyrate concentrations in PO group 3. 5 patients in PO, 4 patients in ME, 6 patients in PO + ME; no serious adverse events related to trial therapy
Greenfield, 1992	UC	43, 3 groups; [8 Olive oil, 16 MaxEPA, 19 SEPO]	RCT Placebo-controlled Double-blinded	Super evening primrose oil [SEPO]; 12 x 250 mg daily for 1 month, 6 x 250 mg for 5 months	Olive oil [Placebo]; 1 g daily for 6 months MaxEPA; 1 g daily for 6 months	6, 9 months	1. Stool frequency 2. Stool consistency 3. Rectal bleeding 4. Relapse 5. Sigmoidoscopic score 6. Histology 7. Laboratory: blood count, sedimentation rate, fatty acid levels in red blood cell membrane	1, 3, 4, 5, 6, 7. n.s. 2. Sig. group difference in stool consistency after 6, 9 months

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
Hanai, 2004	UC	59, 2 groups [22 GBF, 37 ST]	Non-randomized Verum-controlled Open-label	Germinated Barley foodstuff [GBF]; 20 g daily for 12 months; in addition standard treatment [5-ASA/ steroids]	Standard treatment with 5-ASA/ steroids [ST]; for 12 months	3, 6, 9, 12 months	1. Changes in the dose of 5-ASA and steroids 2. CAI 3. Endoscopic score 4. Cumulative recurrence rate	1. Ssig. decrease of steroid use in GBF at 3 months compared with ST 2. Sig. lower CAI in GBF at 3, 6, 12 months compared with ST 3. n.s. 4. Sig. lower rate in GBF compared with ST
Langhorst, 2013	UC	97, 2 groups [48 Myrrhinil, 49 Mesalazine]	RCT Double-blinded Double-dummy	Myrrhinil intest® [oral preparation of 100 mg myrrh, 70 mg chamomile extract, and 50 mg coffee charcoal]	Mesalazine 3 x 500mg	1, 3, 6, 9, 12 months	1. Clinical Colitis Index [CAI] 2. Modified CAI 3. Endoscopic index 4. Fecal markers [lactoferrin, calprotectin, PMN elastase 5. Laboratory [CRP, WBC, HB] 6. Safety	1. No significant group differences 2. No significant group differences 3. No significant group differences 4. No significant group differences 5. No significant group differences 6. 42 [myrrhinil] vs. 49 [mesalazine] patients with adverse events; 10 vs. 8 serious adverse events, no causal relation to therapy

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
Langmead, 2004	Active UC	44, 2 groups [30 AV, 14 Placebo]	RCT Placebo-controlled Double-blinded	Aloe vera gel [AV]; 2 x 100 ml daily for 4 weeks [starting with 25 ml and increasing the dose by 25 ml each time until 100 ml]	Placebo; 2 x 100 ml daily for 4 weeks	2, 4 weeks	1. Remission [SCCAI] 2. Improvement [SCCAI] 3. Physician's global assessment 4. IBDQ 5. Sigmoidoscopic examination 6. Histologic results 7. Laboratory testing: Hb, platelet count, CRP, serum albumin 8. Adverse events	1. n. s. 2. Sig. increase in AV after 4 weeks compared with baseline 3. n. s. 4. Sig. increase in Placebo after 4 weeks compared with baseline 5. n.s. 6. Sig. decrease in histologic score in AV after 4 weeks compared with baseline 7. n.s. 8. 6 patients in AV, 4 patients in Placebo; no serious adverse events
Naftali, 2013	Active CD	22, 2 groups [12 cannabis, 10 Placebo]	RCT Placebo-controlled Double-blinded	Cannabis sativa cigarettes [115 mg THC each], twice daily for 8 weeks	Placebo cannabis cigarettes [<2 mg THC each], twice daily for 8 weeks	2, 8, 10 weeks	1. Remission rate [CDAI] 2. Response rate [CDAI] 3. C-reactive protein 4. Quality of life [SF-36] 5. Side effects	1. n.s. 2. Sig. larger response rate in cannabis [90%] vs. Placebo [40%] 3. n.s. 4. Sig. larger increase in cannabis 5. n.s.
Rastegarpanah, 2012	Inactive UC	80, 2 groups [42 silymarin, 38 Placebo]	RCT Placebo-controlled Double-blinded	Oral silymarin [140 mg] once daily for 6 months	Placebo once daily for 6 months	6 months	1. Hemoglobin 2. Erythrocyte sedimentation rate 3. Symptoms [abdominal pain, diarrhea, fatigue, anorexia, joint or eye complications] 4. Disease activity [DAI] 5. Adverse events	1. Sig. improvement in silymarin group only 2. Sig. improvement in silymarin group only 3. No outcomes reported 4. Sig. improvement in silymarin group only 5. n.s.
Tong, 2011	UC	126, 3 groups [42 CSCC1, 42 CSCC2, 42 ME]	RCT Placebo-controlled Single-blinded?	Sophora Colon Soluble Capsules [CSCC]; CSCC1: 18 x 960 mg CSCC2: 12 x 960 mg daily for 8 weeks	Mesalazine [ME]; 4 x 250 mg daily for 8 weeks	2, 4, 6, 8 weeks	1. Clinical efficacy 2. Fibrocolonoscopic examination 3. Stool sample: red blood cells, white blood cells 4. Safety	1. n.s. 2. n.s. 3. n.s. 4. 3 patients in CSCC1, 2 patients in CSCC2, 2 patients in ME, no serious adverse events

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
MIND/BODY INTERVENTIONS								
Berrill ,2014	IBD	66, 2 groups [33 MCT, 33 SC]	RCT	Multi-convergent Therapy [MCT]; 6 x 40-min sessions over 16 weeks	Standard care [SC]	4, 8, 12 months	1. IBDQ 2. Relapse 3. Medication escalations 4. Perceived stress [PSQ, RDHS] 5. Coping [WCC] 6. Irritable bowel symptoms [IBS-SSS]	1. n.s. 2. n.s. 3. n.s. 4. n.s. 5. n.s. 6. n.s.
Elsenbruch, 2006	UC	30; 2 groups [15 MBSR, 15 WL]	RCT Randomized? [27/30] Waitlist-controlled	MBSR program [MBSR]; 6 h, 1 day a week for 10 weeks	Waiting list control group [WL]; usual care	2 4, 6, 8, 10 weeks	1. Quality of life [IBDQ, SF-36] 2. Perceived stress [PSS] 3. CAI 4. Laboratory lymphocytes, TNF-α, catecholamine, cortisol, prolactin, growth hormones	1. Ssig. improvement in SF-36 Mental Health Scale, Psychological Health Sum Score and IBDQ Bowel Symptoms Scale after 10 weeks in MBSR compared with WL 2. n.s. 3. n.s. **4. n.s**
Jedel, 2014	UC	55, 2 groups [27 MBSR, 28 AC]	RCT	Mindfulness-Based Stress Reduction [MBSR]; 2.5 hours, once weekly + 45 min/ day homework for 8 weeks	Attention control [AC]; once weekly + homework for 8 weeks	2, 6, 12 months	1. Disease status [Mayo UC-DAI] 2. Inflammatory markers [calprotectin, cytokines, CRP] 3. IBDQ 4. Time to flare-up 5. Severity of flare-up [UC-DAI] 6. Markers of stress [ACTH, urinary cortisol] 7. Perceived stress [PSQ] 8. Depression [BDI] 9. Anxiety [STAI] 10. Mindfulness [MAAS] 11. Perceived health competence [PHCS]	1. n.s. 2. n.s. 3. Sig. group difference in bowel subscale and systemic subscale, else n.s.. 4. n.s. 5. n.s. 6. n.s. 7. n.s. 8. n.s. 9. n.s. 10 n.s. 11. n.s.

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
Keefer, 2013	Quiescent UC	54, 2 [26 Hypnotherapy, 29 control group]	RCT	Gut-directed hypnotherapy 7 x 40 min sessions, weekly + home practice for 12 months, 1–2 times weekly	Attention control, discussions about 'the connection between mind and body in UC'	52 weeks	1. Maintenance of clinical remission 2. Quality of life [IBDQ] 3. Quality of life [SF-12] 4. Perceived stress questionnaire [PSQ] 5. Perceived health competence [PHCS] 6. IBD Self Efficacy Scale [IBD-SES] 7. Rating form of IBD Patients [RF-IPC] 8. The medication adherence form [MAS] 9. Adverse effects	1. Sig. more patients in remission in hypnotherapy compared with control, sig. more days to clinical relapse in hypnotherapy 2–8. n.s. 9. No adverse effects
Milne, 1986	IBD	80, 2 groups [40 each]	RCT	Stress management technique: 6 x 3-h training sessions, including planning skills, communication skills, autogenic training	Usual care	4, 8, 12 months	1. CDAI 2. IBD stress index	1. Sig. improvement within the treatment group, but not control group for all time points 2. Sig. improvement within the treatment group, but not control group for all time points
Mizrahi, 2013	IBD	56, 2 groups	RCT	Relaxation training [Relax], 3 sessions and CD for home practice	Waiting control group, usual care	5 weeks	1. Pain [VAS] 2. Anxiety [STAI] 3. QOL [IBDQ] 4. Depression [VAS] 5. Mood [VAS] 6. Stress [VAS]	1. Sig. improvement in relax, but not WL 2. Sig. improvement in relax, but not WL 3. Sig. improvement in relax, but not WL 4. Sig. improvement in relax, but not WL 5. Sig. improvement in relax, but not WL 6. Sig. improvement in relax, but not WL

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
Langhorst, 2007	UC	60, 2 groups	RCT Waitlist-controlled	Life style modification [MBSR]; 6 h, 1 day a week for 10 weeks	Waiting control group, usual care	3, 12 months	1. Quality of life [IBDQ, SF-36] 2. Psychological distress [BSI] 3. CAI 4. Medication change	1. Sig. improvement in SF-36 physical functioning after 3 months in MBSR compared with WL 2. Sig. reduction of BSI anxiety after 3 months in MBSR compared with WL 3. n.s. 4. n.s.
ACUPUNCTURE								
Joos, 2004	Active CD	54, 2 groups [27 TCM, 24 CG]	RCT Sham-controlled Single-blinded	Acupuncture; + moxibustion [TCM]; 10 sessions in 4 weeks	Control group [CG]; Acupuncture at non- acupuncture points, 10 sessions in 4 weeks	4, 12 weeks	1. CDAI 2. Quality of life [IBDQ] 3. General well- being 4. Serum markers of inflammation [α_1-acid glycoprotein, CRP] 5. Adverse events	1. Sig. decrease after 4 weeks in TCM compared with CG 2. n.s. 3. Sig. increase after 4 weeks in TCM compared with CG 4. Sig. decrease in α_1-acid glycoprotein in TCM after 4 weeks compared with baseline 5. 3 patients in TCM unrelated to trial therapy, 2 patients in CG; no serious adverse events

Table 1. Continued

Author	Disease	No of subjects, no of groups	Study type	Intervention	Control / other interventions	Follow-up	Outcome measures	Results
Joos, 2006	Active UC	29, 2 groups [15 TCM, 14 CG]	RCT Sham-controlled Single-blinded	Acupuncture; + moxibustion [TCM]; 10 sessions in 5 weeks	Control group [CG]; Acupuncture at non-acupuncture points, 10 sessions in 5 weeks	5, 16 weeks	1. CAI 2. Quality of life 3. General well- being 4. Serum markers of inflammation	1. Sig. decrease after 5 weeks in TCM compared with CG 2. Sig. increases after 5, 16 weeks in TCM and CG compared with baseline 3. Sig. increases after 5 weeks in TCM and CG compared with baseline 4. n.s.
TRICHURIS SUIS OVA								
Summers, 2005	Active UC	54, 2 groups [30 TSO, 24 Placebo]	RCT Placebo-controlled Double-blinded	Trichuris suis ova [TSO]; 2500x at 2-week intervals for 12 weeks	Placebo	2, 6, 12 weeks	1. UCDAI 2. Remission 3. Clinical Colitis Activity Index 4. Laboratory testing: blood count, erythrocyte sedimentation rate, CRP, liver profile 5. Stool examination: ova, parasites, bacterial pathogens, C difficile toxin 6. Side effects	1. Significant higher response rate in TSO compared with Placebo after 12 weeks 2. n.s. 3. Sig. decrease in TSO compared with Placebo after 8 and 12 weeks 4. n.s. 5. Negative for ova and parasites in TSO 6. 1 in TSO, 3 in Placebo; no serious adverse events related to trial therapy

Suggestions for definitions: CAM, Complementary and Alternative Medicine; IBD, Inflammatory Bowel Disease; CD, Crohn's disease; UC, ulcerative colitis; RCT, Randomized controlled trials; CT, controlled trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines; CDAI, Crohn's disease activity index; CAI, Colitis activity index; TCM, Traditional Chinese Medicine; IBDQ, inflammatory bowel disease questionaire; ASA, Aminosalicylic Acid; SF-36, Short Form (36) Health Survey; PSQ, perceived stress questionnaire; RDHS, Revised Daily Hassle Scale; WCC, Ways of Coping Checklist; BDI, Beck depression inventory; PSS, Perceived stress scale; RF, Rating form of IBD patients; MAAS, Mindful Attention Awareness Scale; VAS, visual analogue scale; STAI, State-Trait-anxiety inventory; QOL, Quality of life; UCDAI, ulcerative colitis disease activity index.

Table 2. Risk of bias assessment of the included studies using the Cochrane risk of bias tool

Bias Author, year	Selection bias:			Performance bias:				Attrition bias:		Reporting bias:	Detection bias:		Total risk: [max. 12] Low risk ≥ 6
	Adequate random sequence generation	Adequate allocation concealment	Similar baseline characteristic	Adequate participant blinding	Adequate provider blinding	Similar or no co-interventions	Acceptable compliance	Acceptable and described drop-out rate	Inclusion of an intention-to-treat analysis	No selective outcome reporting	Adequate outcome assessor blinding	Similar timing of outcome assessment	
HERBS AND BOTANICALS Boswellia serrata													
Gerhard	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	12
Gupta, 1997 CT	n.a.	n.a.	no	no	no	yes	unclear	yes	yes	yes	no	yes	5
Gupta, 2001 CT	n.a.	n.a.	no	no	no	unclear	unclear	no	no	yes	no	yes	2
Holtmeier	yes	yes	yes	yes	yes	yes	unclear	yes	no	yes	yes	yes	10
HERBS AND BOTANICALS Artemisia absinthium													
Krebs	unclear	unclear	yes	No	no	yes	unclear	yes	yes	yes	no	yes	6
Omer	unclear	yes	yes	Yes	yes	yes	yes	yes	yes	yes	yes	yes	11
HERBS AND BOTANICALS Andrographis paniculata													
Sandborn	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	12
Tang	unclear	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes	yes	10
HERBS AND BOTANICALS Curcumin													
Hanai, 2006	yes	yes	yes	yes	yes	yes	unclear	yes	no	yes	yes	yes	10
Singla	yes	yes	yes	yes	yes	yes	unclear	no	yes	yes	yes	yes	10
HERBS AND BOTANICALS Others													
Ben-Arye	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	11
Fernandez-Banares	yes	yes	yes	no	no	yes	yes	no	yes	yes	no	yes	8
Greenfield	unclear	yes	no	no	no	unclear	unclear	yes	no	yes	yes	yes	5
Hanai, 2004 CT	n.a.	n.a.	yes	no	no	yes	unclear	no	no	yes	no	yes	4
Langhorst	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	12
Langmead	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	yes	10
Naftali	unclear	unclear	no	No	yes	yes	unclear	yes	unclear	yes	yes	yes	7
Rastegarpanah	yes	unclear	yes	unclear	unclear	unclear	unclear	yes	no	no	unclear	yes	4
Tong	unclear	unclear	yes	unclear	unclear	unclear	unclear	yes	yes	yes	unclear	yes	5
MIND/BODY MEDICINE													
Berrill	yes	yes	yes	no	no	yes	no	no	no	unclear	unclear	yes	5
Elsenbruch	no	yes	yes	no	no	yes	yes	yes	yes	yes	no	yes	8
Jedel	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes	yes	10

Table 2. Continued

Bias Author, year	Selection bias:			Performance bias:			Attrition bias:		Reporting bias:	Detection bias:		Total risk: [max. 12]
	Adequate random sequence generation	Adequate allocation concealment	Similar baseline characteristic	Adequate participant blinding	Adequate provider blinding	Similar or no co-interventions	Acceptable compliance	Acceptable and described drop-out rate	Inclusion of an intention-to-treat analysis	No selective outcome reporting	Adequate outcome assessor blinding	Similar timing of outcome assessment	Low risk ≥ 6
Keefer	yes	unclear	yes	no	no	unclear	yes	yes	yes	unclear	yes	yes	7
Milne	unclear	unclear	no	no	no	unclear	no	yes	no	yes	yes	yes	4
Mizrahi	unclear	unclear	yes	no	no	yes	unclear	no	no	yes	unclear	yes	4
Langhorst	yes	no	yes	no	no	yes	yes	yes	yes	yes	no	yes	8
ACUPUNCTURE													
Joos, 2004	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes	10
Joos, 2006	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes	10
Trichuris suis ova													
Summers	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	12

[a]Additional details provided upon request.
[b]1 patient excluded.
n.a., not applicable.

Holtmeier et al.[36] investigated a boswellia extract in a double blind placebo-controlled study in 82 patients with Crohn's disease in remission. After 12 months there was no significant difference regarding maintenance of remission, relapse time, or severity of symptoms. Adverse events were reported in equal amount for both groups, none of which was regarded as of serious magnitude.

Study quality was diverse for boswellia serrata, with two studies having high risk of bias,[32,33] and two studies with high scores.[30,36] The main weaknesses of the studies were the heterogeneity of the sample in the non-randomized samples,[32,33] high drop-out rates[36] or the missing explanations/analysis of drop-outs,[32,33] and the short follow-up periods.[30,32,33]

3.1.3. Artemisia absinthium [wormwood]

Two randomized controlled trials[41,48] investigated the effect of wormwood in active Crohn's disease. Twenty patients were treated with standard treatment alone or with additional artemisia absinthium for 6 weeks in an open-label fashion.[41] Patients in the intervention group showed significant decrease in disease activity and depression, and an increase in quality of life after 6 weeks. No such differences were found within the control group. The study also found significant reduction of TNF-α [tumor necrosis factor alpha] within the intervention group.

Omer et al.[48] compared the efficacy of wormwood to a placebo, on top of a steroid or prednisolone treatment which was gradually reduced until patients were free of steroids at Week 10. Forty patients were followed for up to 20 weeks; outcomes included severity of symptoms, quality of life, depression, and subjective well-being. At Weeks 6, 8, and 20, the intervention group reported significantly less symptoms, and increased well-being at Weeks 8, 10 and 12. No further differences were observed.

Study quality was mixed. The biggest concerns were non-randomization,[41] missing blinding,[41] the short observational period,[41,48] and the non-reporting of adverse events.

3.1.4. Andrographis paniculata [Indian echinacea]

A total of 120 patients with active ulcerative colitis were studied in a randomized double-blinded trial by Tang.[53] Patients in the intervention group received 8 weeks of HMPL-004, which contains an andrographis paniculata extract, whereas the control group received mesalazine. Clinical symptom severity and endoscopic and histological signs were assessed every 2 weeks. Results revealed that both groups showed significant improvements on all outcomes. Side effects were twice as prevalent in the mesalazine group compared with the intervention group, occurring in 27% and 13% of the patients, respectively. Although the study quality was relatively high, the authors did not describe the randomization procedure nor the compliance.

Another trial by Sandborn and colleagues[50] investigated the effects of andrographis paniculata extract HMPL-004 in patients with active ulcerative colitis; 224 patients were randomized to either 1200 mg or 1800 mg of the trial medication or to placebo. All patients also received stable doses of mesalamine. Outcomes were assessed after 8 weeks. Patients receiving andrographis paniculata showed significant higher response rates, but no differences between the doses were found. Remission rates were also similar between the groups. Except for mild rashes, which were more common in the intervention groups, no differences regarding adverse events were found. Quality of the trials was very high.

3.1.5. Curcumin

Hanai[34] compared curcumin with placebo in addition to sulfasalazine for maintenance of remission in ulcerative colitis; 89 patients were randomly assigned, and patients as well as providers were blinded. Treatment lasted 6 months and clinical and endoscopic disease activity, recurrence rate, and adverse events were tested up to 12 months. Results showed significantly less disease activity and lower recurrence rate at 6 months in the verum group. No serious adverse events were observed in the study. The risk of bias of the study was considered low.

Another study with low risk of bias compared curcumin enema combined with oral mesalamine with placebo enema combined with oral mesalamine, in 45 patients with distal ulcerative colitis with mild-to-moderate disease activity.[51] At 8 weeks, this study found no significant differences regarding disease activity or remission rate when analyzing the intention-to-treat population. No severe adverse events occurred.

3.1.6. Wheatgrass juice

Wheat grass juice vs. placebo was compared in a randomized double-blind study[26] in patients with active ulcerative colitis; 24 patients were evaluated by means of disease activity, symptoms severity, and adverse events. After 4 weeks of wheat grass juice administration, patients showed significantly less disease activity, less rectal bleeding and less abdominal pain. Physician's global assessment was also in favor of the intervention group. No serious adverse events were observed. Risk of bias was very low, but analysis did not include drop-outs, and follow-up was too short. Blinding on the other hand was very well described and the authors also checked the credibility of the blinding at the end of the study.

3.1.7. Plantago ovata [Desert Indian wheat]

Plantago ovata [PO] seeds, mesalamine, or a combination of both were studied in patients with ulcerative colitis in remission, by Fernandez-Banares.[29]

Patients [n = 102] were randomly allocated to intervention or two control groups, and they were monitored for up to 12 months. Maintenance of remission after 12 months did not reveal significant differences. Patients in the PO group showed increased butyrate concentrations in the stool, but no serious adverse events were observed. The study had a low risk of bias, but blinding, reporting, and analysis of drop-outs were inadequate.

3.1.8. Super evening primrose oil

Greenfield et al.[31] compared the efficacy of evening primrose oil on active ulcerative colitis with placebo [olive oil] and high-dose omega-3 oil. Treatment lasted 6 months and outcomes were assessed at 6 and 9 months for 43 patients. Besides stool consistency after 6 and 9 months, no further significant differences could be observed. Adverse events were not reported. The study has a low risk of bias, but randomization was not adequately described, and blinding was not appropriately done.

3.1.9. Germinated barley

Hanai[35] compared standard therapy alone with standard therapy plus germinated barley foodstuff for 12 months. Group allocation for the 59 patients with ulcerative colitis was not randomized and neither patients nor providers were blinded. After 3 months, patients in the combined group showed significant decrease of steroid use, and after 3, 6 and 12 months the severity of clinical symptoms and recurrence of UC in those achieving remission was significantly lower in the intervention group. Risk of bias was rather high, with the main deficiencies being lacks of randomization, blinding, analysis of drop-outs, and reporting of adverse events.

3.1.10. Myrrh, chamomile extract, and coffee charcoal

A combination of myrrh, chamomile extract, and coffee charcoal [Myrrhinil intest®] was tested in a double-blind double-dummy RCT by Langhorst et al.[43] A total of 97 patients received either Myrrhinil intest ® or mesalazine for 12 months. Analysis revealed that the preparation was not inferior to mesalazine regarding clinical outcomes and safety. The trial was judged to have a very low risk of bias.

3.1.11. Aloe vera gel

A total of 44 with active ulcerative colitis were included in this double-blind placebo-controlled study.[44] Two-thirds of the patients were randomized to the aloe vera group and received 4 weeks of aloe vera gel at increasing doses. Remission, symptoms severity, physician's global assessment, quality of life, and laboratory measures were taken at 2 and 4 weeks. The intervention group showed significant improvements in clinical signs and quality of life at 4 weeks compared with baseline, with a reduction in histologic score as well. No serious adverse events were reported. The study was judged to have low risk of bias.

3.1.12. Cannabis

One double-blind study compared cannabis sativa cigarettes with placebo cigarettes from which tetra-hydrocannabinol [THC] was removed, in 22 patients with active Crohn's disease.[47] This study found significant group differences favoring cannabis over placebo for response rate [>100 reduction in Crohn´s disease activity index [CDAI] scores], and quality of life, but not for remission rate [CDAI <150] or reduction of C-reactive protein. Side effects did not differ significantly between groups. Whereas this study had a low overall risk of bias, randomization and allocation procedure was insufficiently reported and blinding of participants failed.

3.1.13. Silymarin

One study assessed the effects of oral silymarin compared with placebo in 80 patients with inactive ulcerative colitis.[49] Whereas hemoglobin levels, erythrocyte sedimentation rate, and disease activity significantly improved in the silymarin group but not in the placebo group, no group differences were reported. Incidence of adverse reactions did not change in either group. The study had high risk of bias.

3.1.14. Sophora [Japanese pagoda tree]

Tong et al.[54] investigated the effect of sophora colon-soluble capsules compared with mesalazine, which were administered in a single-blind fashion. Two different doses of sophora were tested. The study duration was 8 weeks; outcomes were assessed every2 weeks in 126 patients with ulcerative colitis. Results revealed no significant differences between groups regarding disease activity or laboratory measurements. No serious adverse events were observed. Risk of bias was low; the main concerns regarded missing description of randomization and allocation, blinding methods, and compliance as well as a short observational period.

3.2. Mind/body medicine

3.2.1. Lifestyle modification

Two studies investigated the effect of lifestyle modification programs on disease activity, quality of life, psychological parameters and laboratory profiles[28,42] in 30[28] and 60[42] patients with ulcerative

colitis. Both studies applied a randomized wait-list controlled study design. The programs lasted 10 weeks each and outcomes were assessed after 10 weeks[28] or 3 and 12 months.[42] Results showed significant improvement in psychological quality of life after 10 weeks[28] and 3 months,[42] as well as significant reduction of anxiety after 3 months.[42] Neither medication nor laboratory profiles showed any change. Risk of bias was low in both studies. In one study, however, the randomization had to be criticized, because three patients changed groups after allocation.

3.2.2. Mindfulness-based interventions

Two further studies investigated the effects of mindfulness-based interventions on 66 patients with either inactive ulcerative colitis or Crohn's disease,[27] and on 55 patients with inactive ulcerative colitis. [37] One study compared one-to-one multi-convergent therapy plus standard care with standard care alone,[27] and the other study compared mindfulness-based stress reduction courses with time/attention control courses.[37] Whereas no study showed significant group differences regarding disease activity, relapse, or psychological variables in the main analysis, significant effects on quality of life were found in patients with additional irritable bowel syndrome-type symptoms,[27] and also effects on stress and C-reactive protein in patients who flared during the course of the study.[37] Risk of bias was high in one study[27] and low in the other.[37]

3.2.3. Hypnotherapy

Keefer et al.[40] investigated the effects of gut-directed hypnotherapy, a program that was developed for irritable bowel syndrome. Patients received 7 weekly sessions of hypnotherapy compared with an attention/control group, and after 52 weeks they were significantly better regarding probability of flare. However, no effects were found for quality of life or other psychological measures. The risk of bias in the trial was low.

3.2.4. Mindfulness-based interventions

A study by Milne et al.[45] compared the effects of a stress management technique with usual care in 80 patients with IBD. The training included 6 x 3 h of training in individual planning skills, communication skills, and autogenic training. After 4, 8, and 12 months, patients in the stress management group but not in the control group showed significant improvements in symptoms and stress. Risk of bias however was high, especially in randomization and allocation as well as in compliance, and appropriate dealing with drop-outs was insufficient.

3.2.5. Relaxation training

A study by Mizrahi et al.[46] investigated the effects of relaxation training in patients with IBD in general; 56 patients were randomized to three sessions following home practice of relaxation or to a usual-care group. The authors found significant improvements in pain, anxiety, depression, mood, stress, and quality of life including bowel symptoms, within the relaxation group, but not in the usual-care group. Risk of bias was high in this study as it failed to report random allocation procedure and no attempt was made to blind patients or outcome assessors.

3.2.6. Acupuncture and moxibustion

Two studies by Joos et al.[38,39] were included in the review. The former investigated 51 patients with active Crohn's disease, and the latter did so with 29 patients with ulcerative colitis. In the colitis study, the a priori calculated number of patients could not be reached. Treatment included 10 sessions within 4 weeks[38] or 5 weeks,[39] and the control used acupuncture at non-acupuncture points. Clinical disease activity, quality of life, and well-being, as well as serum markers of inflammation, were measured after 4 and 12[38] or 5 and 16 weeks.[39] Significant decreases in disease activity and increase in well-being were observed after 4 and 5 weeks, respectively.[38] Quality of life increased in the intervention and in the control group after 5 and 16 weeks,[39] but no differences between the groups at either time point were observed. No serious adverse events were observed. Risk of bias was low, though it could have been improved by blinded outcome assessors.

3.2.7. Trichuris suis ova

Trichuris suis ova, ie whipworm eggs, were tested by Summers et al.[52] in a randomized placebo-controlled double-blind trial on active ulcerative colitis. Treatment included intake of the therapeutic agent for 12 weeks at 2-week intervals. Every 2 weeks the disease activity, remission, and laboratory measures were taken. Results revealed that higher response rates but not remission rates were observed regarding disease activity in the intervention group compared with placebo after 12 weeks. No serious adverse event was observed in this trial. The risk of bias was very low, and the study received full points for every criterion.

4. Discussion

This review found evidence from 29 trials on complementary and alternative therapies in the treatment of inflammatory bowel diseases. Whereas most studies tested the effects of herbal medicine and botanicals, there were also a large number of trials available for mind/body or psychological interventions, as well as acupuncture trials and a trial utilizing helminths. For most interventions no more than one or two trials were available. The risk of bias was quite heterogeneous among the trials.

4.1. Interpretation

4.1.1. Herbs and botanicals

The treatment with herbal preparations containing a variety of potential effective ingredients offers a possible multi-target approach. However, the huge range of biologically active compounds may even result in adverse effects. Based on in vitro studies, numerous individual chemicals derived from several different plants may have antibacterial, antioxidant, anticytokine, antispasmodic, and neuromodulatory actions.[44] Of more importance, a variety of herbs show first evidence with performance at least equal to conventional treatment alone, or superior to placebo when used as complementary to conventional treatment in clinical studies. Most of these herbal therapies have been reported to have plausible mechanisms of action in IBD. For example, in vitro as well as small in vivo studies have shown the suppression of TNF-α by wormwood compared with placebo.[41] Andrographis paniculata shows inhibiting potential against TNF- α, IL-1ß, and NF-KB in an in vitro setting.[50]

Boswellic acid, the major constituent of boswellia, was shown to inhibit NF-KB signaling pathways in macrophages in mouse model of psoriasis, markedly decreasing the production of the pro-inflammatory key cytokine TNF- α and the chemokine MCP-1.[55] In addition, in vitro studies and animal models show that boswellic acid inhibits

5-lipoxygenase selectively[56] and has anti-inflammatory[57] and anti-proliferative effects.[58] Unlike other non-steroidal anti-inflammatory drugs, however, boswellic acid fails to show analgesic or antipyretic effects.[59] In addition, it does not cause gastric ulcers in animals. This suggests that the action of boswellic acid is likely through mechanisms other than the inhibition of prostaglandin synthesis.

Myrrh resin, Commiphora molmol, with its main ingredients furanosesesquiterpene, diterpenacids, and volatile acids, has anti-inflammatory, antiphlogistic, antioxidant, antibacterial, and astringent potential.[60–63]

Chamomile dry extract of chamomile flowers, with its main ingredients volatile acids, flavonglykosides, and hydroxycumarines, has anti-inflammatory effects and has antibacterial, spasmolytic, and ulcer-protective potential.[64–67] The combination has shown first promising evidence in maintenance therapy of ulcerative colitis.[43]

Cannabinoids were found to ameliorate inflammation in a mouse model of colitis.[68] An anti-inflammatory effect of cannabinoids, mainly through the cannabinoid 2 receptor, has been stated. Cannabinoid exposure antagonizes release of prostaglandins, histamine, and the matrix-active proteases from mast cells.[69] The phagocytic function of macrophages is suppressed by cannabinoid exposure. It also suppresses inflammation by down-regulating the production of cytokines such as TNF- α , interferon-g, and interleukin-1.[70] Of interest, in the clinical trial of Naftali et al.,[47] cannabis was administered by smoking, tp obtain the rapid induction of an increase in blood cannabinoid levels. During smoking, the acids are decarboxylated to the active free cannabinoids. Conversely, ingesting cannabis orally is less effective than smoking.

However, the variety of drug formulations and missing dosages in studies limit the benefit of information. In addition, most of the introduced herbs and botanicals have a registration as food supplements, and some have an approval as pharmaceuticals, influencing the quality of the products. In the case of cannabis, additional special restrictions to availability may be of importance. In addition, it has to be clarified whether a proposed treatment success is caused by a relief of symptoms like pain, or ntiemetic effects, or improved appetite, or sleep, rather than an by anti-inflammatory effect or by a combination of both.

Several other drugs, like bilberry with its mayor component anthocyanin, have been shown to have anti-inflammatory potential in vitro and in vivo[20] but no randomized controlled trials were found. Therefore, they were not included in this paper.

4.1.2. Mind/body medicine

Perceived stress is a significant predictor for flaring in UC,[71–73] and the risk of experiencing exacerbation is multiplied by prolonged exposure to stress.[74] Up to 70% of patients with inflammatory bowel disease regard stress as modifying for their disease, and 85% regard sufficient coping as having a positive impact on their course of disease.[8,42] Therefore, studies testing effects of different interventions targeting stress and psychological well-being on the course of disease are urgently warranted.

First studies in the field of relaxation training introduce improvements on several side effects and psychosocial components in IBD and, in the field of hypnotherapy, effects on maintenance therapy in UC. However, additional confirming studies are yet to come. Furthermore, the currently available studies[28,37,42] in mindfulness-based stress reduction [MBSR] are clearly not powered sufficiently to give a conclusive answer as to whether it is effective for maintenance treatment and prevention of relapse in ulcerative colitis. However, a high compliance and no relevant side effects were described. Positive brief effects occurred for health-related quality of life. Although patients do not benefit in general in terms of disease activity or laboratory parameters, the results of the study of Jedel et al.[37] indicate that a subgroup of patients, namely those with higher stress levels, actually do. This might be of special importance in individuals with heightened physiological responses to stress, in whom MBSR interventions might prevent flare-up by minimizing the impact of stress on inflammatory cascades. In addition, mind/body interventions might actually be able to turn patients' and practitioners' perspectives away from a purely pathogenetical view to complementary salutogenetic approaches. Patients in the MBSR intervention group demonstrated significantly better quality of life during a flare compared with flared controls. This quite unique finding introduces a new quality of treatment, improving patients' resources and preparing them while in remission for significantly better coping with disease in the event of a flare, to decrease the burden of disease. These findings are of special interest and should be evaluated in depth in the near future.

4.1.3. Traditional Chinese Medicine [TCM]/acupuncture

Acupuncture has been used for thousands of years to treat various medical conditions. It has been shown to be effective for treating various pain and gastrointestinal disorders, particularly nausea due to operation, chemotherapy, pregnancy, and motion sickness.[75–77]

In IBD, the two studies of Joos et al.[38,39] show first evidence for a complementary therapeutic effect with regard to disease activity scores, but not to quality of life questionnaires or symptom scores of acupuncture and moxibustion, in active Crohn´s disease as well as ulcerative colitis, using an appealing methodology. Conversely,, Ji et al.[78] give an overview of 43 studies, including 37 in Chinese language. Of note, the modified Jadad quality scale assessing the methodological quality of these studies demonstrated a score of 1 or 2 in a total of 39 studies, demonstrating inacceptable low methodical standards, ie major methodological deficiencies including insufficient description of endpoints and randomization process, and missing power calculations. Assumed psychoneuroimmunologic pathways, influenced by acupuncture as explanation for the presumed acupuncture effects in Crohn's and colitis patients, have not been proven yet.

A review by Lee et al.[79] included five Chinese studies and found favorable effects of moxibustion on the response rate compared with conventional drug therapy, with a risk ratio of 1.24. Quality of the included studies was low and the authors assume that results are inconclusive due to the high risk of bias observed.

Further high quality research is mandatory to provide higher levels of evidence in the field of acupuncture and TCM.

4.1.4. Trichuris suis ova

Some epidemiologic studies suggest that helminth infection in childhood protects against development of inflammatory bowel disease [IBD] in later years.[80] In addition, helminths have shown protective effects and changed gut bacterial flora in animal models.[80] Consequently, first studies with trichuris suis ova, ie whipworm eggs, showed some positive treatment effects in ulcerative colitis as well as Crohn´s disease. The treatment was rated as safe, which was lately further confirmed by a small study of Sandborn et al.[25] Currently, two large randomized placebo-controlled multi-center trials in Crohn's disease, one in North America and one in Europe, have been reported in the press as being negative; whereas a study in UC is ongoing.

4.2. Limitations

This review has several limitations. First, due to the selection of trials published in English or German only, trials of traditional chinese medicine were not considered. The validity of findings is further limited by the small number of trials, rendering meta-analyses impossible. Many interventions have not been subjected to randomized trials or even to studies on humans. Furthermore, most trials tested interventions for ulcerative colitis; therefore conclusions are mainly limited to patients with ulcerative colitis.

Finally, several systematic reviews and meta-analyses have been published recently,[81,82] but these have mainly focussed on herbal medicines, and they have not used detailed risk of bias assessment. Although they included trials in languages other than English and German, the absolute number of trials was not that much higher. The recent review, however, was also not limited to herbal medicines compared to the search in the here presented study; it is therefore more comprehensive and potentially relevant for researchers and clinicians.

4.3. Conclusion

Addressing the fact that IBD are caused and upheld by multifactorial processes, which include genetic predisposition, immune dysregulation, barrier dysfunction and altered microbial flora,[83–85] as well as environmental and lifestyle factors, it seems plausible that subgroups of patients might benefit from a tailored therapy with emphasis on individually differing modalities.

Whereas the various herbal treatment approaches in principle are using the same pathogenetic paradigm as conventional pharmacotherapy, TCM/acupuncture and, especially, mind/body medicine widen the spectrum of therapy and add a resource-orientated salutogenetic dimension to introduce a multimodal integrative treatment approach.

Patients try to find the most effective and safest therapy for their disorder, including every available option for treatment. In this context, they are likely to perceive CAM and mainstream medicine as equally available treatment options, and to exercise their freedom of choice on their way to a consumer-driven optimal treatment.[8]

A more individualized multimodal treatment approach and further high-quality designs in health research are warranted, to help tailor the right individualized treatment modalities for IBD patients, include salutogenetic approaches like MBSR, and appropriate trials to picture these.

Conflict of interest statement

None declared.

Acknowledgment

This review was supported by the Rut- und Klaus-Bahlsen-Foundation.

References

1. Bensoussan M, Jovenin N, Garcia B, *et al.* Complementary and alternative medicine use by patients with inflammatory bowel disease: results from a postal survey. *Gastroenterol Clin Biol* 2006;**30**:14–23.
2. Burgmann T, Rawsthorne P, Bernstein CN. Predictors of alternative and complementary medicine use in inflammatory bowel disease: do measures of conventional health care utilization relate to use? *Am J Gastroenterol* 2004;**99**:889–93.
3. Hilsden RJ, Meddings JB, Verhoef MJ. Complementary and alternative medicine use by patients with inflammatory bowel disease: An Internet survey. *Can J Gastroenterol* 1999;**13**:327–32.
4. Hilsden RJ, Scott CM, Verhoef MJ. Complementary medicine use by patients with inflammatory bowel disease. *Am J Gastroenterol* 1998;**93**:697–701.
5. Hilsden RJ, Verhoef MJ, Best A, Pocobelli G: Complementary and alternative medicine use by Canadian patients with inflammatory bowel disease: results from a national survey. *Am J Gastroenterol* 2003;**98**:1563–8.
6. Hilsden RJ, Verhoef MJ, Rasmussen H, Porcino A, DeBruyn JC. Use of complementary and alternative medicine by patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**:655–62.
7. Kong SC, Hurlstone DP, Pocock CY, *et al.* The incidence of self-prescribed oral complementary and alternative medicine use by patients with gastrointestinal diseases. *J Clin Gastroenterol* 2005;**39**:138–41.
8. Langhorst J, Anthonisen IB, Steder-Neukamm U, *et al.* Amount of systemic steroid medication is a strong predictor for the use of complementary and alternative medicine in patients with inflammatory bowel disease: results from a German national survey. *Inflamm Bowel Dis* 2005;**11**:287–95.
9. Rawsthorne P, Shanahan F, Cronin NC, *et al.* An international survey of the use and attitudes regarding alternative medicine by patients with inflammatory bowel disease. *Am J Gastroenterol* 1999;**94**:1298–303.
10. Eisenberg DM, Davis RB, Ettner SL, *et al.* Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998;**280**:1569–75.
11. Zollman C, Vickers A. ABC of complementary medicine. Users and practitioners of complementary medicine. *BMJ* 1999;**319**:836–8.
12. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Rep* 2008 Dec 10;1–23.
13. Callahan LF, Wiley-Exley EK, Mielenz TJ, *et al.* Use of complementary and alternative medicine among patients with arthritis. *Prev Chronic Dis* 2009;**6**:A44.
14. Ferrucci LM, Bell BP, Dhotre KB, *et al.* Complementary and alternative medicine use in chronic liver disease patients. *J Clin Gastroenterol* 2010;**44**:e40–5.
15. Shaw A, Noble A, Salisbury C, Sharp D, Thompson E, Peters TJ. Predictors of complementary therapy use among asthma patients: results of a primary care survey. *Health Soc Care Community* 2008;16:155–64.
16. National Center for Complementary and Alternative Medicine. *What is CAM Medicine?* Bethesda, MD: NCCAM Publication; 2007; No. D347.
17. Katz J, Weinberg L. Complementary medicine use by patients with inflammatory bowel disease. *Am J Gastroenterol* 1998;**93**:673–5.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.
19. Furlan AD, Pennick V, Bombardier C, van Tulder M, Editorial Board CBRG. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;**34**:1929–41.
20. Biedermann L, Mwinyi J, Scharl M, *et al.* Bilberry ingestion improves disease activity in mild to moderate ulcerative colitis an open pilot study. *J Crohns Colitis* 2013;**7**:271–9.
21. Chen Q, Zhang H. Clinical study on 118 cases of ulcerative colitis treated by integration of traditional Chinese and Western medicine. *J Tradit Chin Med* 1999;**19**:163–5.
22. Cozzi F, Podswiadek M, Cardinale G, *et al.* Mud-bath treatment in spondylitis associated with inflammatory bowel disease a pilot randomized clinical trial. *Joint Bone Spine* 2007;**74**:436–9.
23. Hong-Bin W, Hong-Wei J. Clinical study of ulcerative colitis treated by integrated traditional Chinese and Western medicine. *Int Rev Allergol Clin Immunol* 2004;**10**:25–7.
24. Huber R, Ditfurth AV, Amann F, *et al.* Tormentil for active ulcerative colitis: an open-label, dose-escalating study. *J Clin Gastroenterol* 2007;**41**:834–8.
25. Sandborn WJ, Elliott DE, Weinstock J, *et al.* Randomized clinical trial: the safety and tolerability of Trichuris suis ova in patients with Crohn's disease. *Aliment Pharmacol Ther* 2013;**38**:255–63.
26. Ben-Arye E, Goldin E, Wengrower D, Stamper A, Kohn R, Berry E. Wheat grass juice in the treatment of active distal ulcerative colitis: a randomized double-blind placebo-controlled trial. *Scand J Gastroenterol* 2002;**37**:444–9.
27. Berrill JW, Sadlier M, Hood K, Green JT. Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. *J Crohns Colitis* 2014 Sep 1;**8**(9):945–55.

28. Elsenbruch S, Langhorst J, Popkirowa K, *et al.* Effects of mind/body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. *Psychother Psychosom* 2005;**74**:277–87.
29. Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana JL, *et al.* Randomized clinical trial of Plantago ovata seeds [dietary fiber] as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis [GETECCU]. *Am J Gastroenterol* 1999;**94**:427–33.
30. Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R: [Therapy of active Crohn disease with Boswellia serrata extract H 15]. *Z Gastroenterol* 2001;**39**:11–7.
31. Greenfield SM, Green AT, Teare JP, *et al.* A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Aliment Pharmacol Ther* 1993;**7**:159–66.
32. Gupta I, Parihar A, Malhotra P, *et al.* Effects of gum resin of Boswellia serrata in patients with chronic colitis. *Planta Med* 2001;**67**:391–5.
33. Gupta I, Parihar A, Malhotra P, *et al.* Effects of Boswellia serrata gum resin in patients with ulcerative colitis. *Eur J Med Res* 1997;**2**:37–43.
34. Hanai H, Iida T, Takeuchi K, *et al.* Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2006;**4**:1502–6.
35. Hanai H, Kanauchi O, Mitsuyama K, *et al.* Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. *Int J Mol Med* 2004;**13**:643–7.
36. Holtmeier W, Zeuzem S, Preiss J, *et al.* Randomized, placebo-controlled, double-blind trial of Boswellia serrata in maintaining remission of Crohn's disease: good safety profile but lack of efficacy. *Inflamm Bowel Dis* 2011;**17**:573–82.
37. Jedel S, Hoffman A, Merriman P, *et al.* A randomized controlled trial of mindfulness-based stress reduction to prevent flare-up in patients with inactive ulcerative colitis. *Digestion* 2014;**89**:142–55.
38. Joos S, Brinkhaus B, Maluche C, *et al.* Acupuncture and moxibustion in the treatment of active Crohn's disease: a randomized controlled study. *Digestion* 2004;**69**:131–9.
39. Joos S, Wildau N, Kohnen R, *et al.* Acupuncture and moxibustion in the treatment of ulcerative colitis: a randomized controlled study. *Scand J Gastroenterol* 2006;**41**:1056–63.
40. Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. *Aliment Pharmacol Ther* 2013;**38**:761–71.
41. Krebs S, Omer B, Omer TN, Fliser D. Wormwood [Artemisia absinthium] for poorly responsive early-stage IgA nephropathy: a pilot uncontrolled trial. *Am J Kidney Dis* 2010;**56**:1095–9.
42. Langhorst J, Mueller T, Luedtke R, *et al.* Effects of a comprehensive lifestyle modification program on quality-of-life in patients with ulcerative colitis: a twelve-month follow-up. *Scand J Gastroenterol* 2007;**42**:734–45.
43. Langhorst J, Varnhagen I, Schneider SB, *et al.* Randomized clinical trial: a herbal preparation of myrrh, chamomile and coffee charcoal compared with mesalazine in maintaining remission in ulcerative colitis – a double-blind, double-dummy study. *Aliment Pharmacol Ther* 2013;**38**:490–500.
44. Langmead L, Feakins RM, Goldthorpe S, *et al.* Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther* 2004;**19**:739–47.
45. Milne B, Joachim G, Niedhardt J. A stress management programme for inflammatory bowel disease patients. *J Adv Nurs* 1986;**11**:561–7.
46. Mizrahi MC, Reicher-Atir R, Levy S, *et al.* Effects of guided imagery with relaxation training on anxiety and quality of life among patients with inflammatory bowel disease. *Psychol Health* 2012;**27**:1463–79.
47. Naftali T, Bar-Lev Schleider L, Dotan I, *et al.* Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol* 2013;**11**:1276–80 e1.
48. Omer B, Krebs S, Omer H, Noor TO. Steroid-sparing effect of wormwood [Artemisia absinthium] in Crohn's disease: a double-blind placebo-controlled study. *Phytomedicine* 2007;**14**:87–95.
49. Rastegarpanah M, Malekzadeh R, Vahedi H, *et al.* A randomized, double blinded, placebo-controlled clinical trial of silymarin in ulcerative colitis. *Chin J Integr Med* 2012 Apr 11. [Epub ahead of print].
50. Sandborn WJ, Targan SR, Byers VS, *et al.* Andrographis paniculata extract [HMPL-004] for active ulcerative colitis. *Am J Gastroenterol* 2013;**108**:90–8.
51. Singla V, Pratap Mouli V, Garg SK, *et al.* Ahuja V: Induction with NCB-02 [curcumin] enema for mild-to-moderate distal ulcerative colitis – a randomized, placebo-controlled, pilot study. *J Crohns Colitis* 2014;**8**:208–14.
52. Summers RW, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* 2005;**128**:825–32.
53. Tang T, Targan SR, Li ZS, Xu C, Byers VS, Sandborn WJ. Randomized clinical trial: herbal extract HMPL-004 in active ulcerative colitis – a double-blind comparison with sustained release mesalazine. *Aliment Pharmacol Ther* 2011;**33**:194–202.
54. Tong ZQ, Yang B, Chen BY, Zhao ML. A multi-center, randomized, single-blind, controlled clinical study on the efficacy of composite sophora colon-soluble capsules in treating ulcerative colitis. *Chin J Integr Med* 2010;**16**:486–92.
55. Wang H, Syrovets T, Kess D, *et al.* Targeting NF-kappa B with a natural triterpenoid alleviates skin inflammation in a mouse model of psoriasis. *J Immunol* 2009;**183**:4755–63.
56. Dahmen U, Gu YL, Dirsch O, *et al.* Boswellic acid, a potent antiinflammatory drug, inhibits rejection to the same extent as high dose steroids. *Transplant Proc* 2001;**33**:539–41.
57. Madisch A, Miehlke S, Eichele O, *et al.* Boswellia serrata extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. *Int J Colorectal Dis* 2007;**22**:1445–51.
58. Safayhi H, Boden SE, Schweizer S, Ammon HP. Concentration-dependent potentiating and inhibitory effects of Boswellia extracts on 5-lipoxygenase product formation in stimulated PMNL. *Planta Med* 2000;**66**:110–3.
59. Singh GB, Atal CK. Pharmacology of an extract of salai guggal ex-Boswellia serrata, a new non-steroidal anti-inflammatory agent. *Agents Actions* 1986;**18**:407–12.
60. Dolara P, Corte B, Ghelardini C, *et al.* Local anaesthetic, antibacterial and antifungal properties of sesquiterpenes from myrrh. *Planta Med* 2000;**66**:356–8.
61. Isaac O. (Pharmacological investigations with compounds of chamomile i. on the pharmacology of [-]-alpha-bisabolol and bisabolol oxides. Review.) [Author's translation.]. *Planta Med* 1979;35:118–24.
62. Tariq M, Ageel AM, Al-Yahya MA, Mossa JS, Al-Said MS, Parmar NS. Anti-inflammatory activity of Commiphora molmol. *Agents Actions* 1986;**17**:381–2.
63. Zhu N, Sheng S, Sang S, Rosen RT, Ho CT. Isolation and characterization of several aromatic sesquiterpenes from Commiphora myrrha. *Flav Fragr J* 2003;**18**:282–85.
64. Achterrath-Tuckermann U, Kunde R, Flaskamp E, Isaac O, Thiemer K. [Pharmacological investigations with compounds of chamomile. V. Investigations on the spasmolytic effect of compounds of chamomile and Kamillosan on the isolated guinea pig ileum.] *Planta Med* 1980;**39**:38–50.
65. Della Loggia R, Carle R, Sosa S, *et al.* Evaluation of anti-inflammatory activity of chamomile preparations. *Planta Med* 1990;**56**:657–8.
66. Jakovlev V, Isaac O, Thiemer K, Kunde R. (Pharmacological investigations with compounds of chamomile ii. New investigations on the antiphlogistic effects of [-]-alpha-bisabolol and bisabolol oxides.) [Author's translation.] *Planta Med* 1979;**35**:125–40.
67. Safayhi H, Sabieraj J, Sailer ER, Ammon HP. Chamazulene: an antioxidant-type inhibitor of leukotriene B4 formation. *Planta Med* 1994;**60**:410–3.
68. Storr MA, Keenan CM, Zhang H, Patel KD, Makriyannis A, Sharkey KA. Activation of the cannabinoid 2 receptor [CB2] protects against experimental colitis. *Inflamm Bowel Dis* 2009;**15**:1678–85.
69. Small-Howard AL, Shimoda LM, Adra CN, Turner H. Anti-inflammatory potential of CB1-mediated cAMP elevation in mast cells. *Biochem J* 2005;388:465–73.
70. Berdyshev EV. Cannabinoid receptors and the regulation of immune response. *Chem Phys Lipids* 2000;**108**:169–90.
71. Bernstein CN, Singh S, Graff LA, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol* 2010;**105**:1994–2002.
72. Bitton A, Dobkin PL, Edwardes MD, *et al.* Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut* 2008;**57**:1386–92.

73. Langhorst J, Hofstetter A, Wolfe F, Hauser W: Short-term stress, but not mucosal healing nor depression was predictive for the risk of relapse in patients with ulcerative colitis: a prospective 12-month follow-up study. *Inflamm Bowel Dis* 2013;**19**:2380–6.
74. Levenstein S, Prantera C, Varvo V, *et al.* Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000;**95**:1213–20.
75. Lao L, Zhang G, Wong RH, Carter AK, Wynn RL, Berman BM. The effect of electroacupuncture as an adjunct on cyclophosphamide-induced emesis in ferrets. *Pharmacol Biochem Behav* 2003;**74**:691–9.
76. Vickers AJ. Can acupuncture have specific effects on health? A systematic review of acupuncture antiemesis trials. *J R Soc Med* 1996;**89**:303–11.
77. Garcia MK, McQuade J, Haddad R, Patel S, Lee R, Yang P, Palmer JL, Cohen L. Systematic review of acupuncture in cancer care: a synthesis of the evidence. *J Clin Oncol* 2013 Mar 1;**31**(7):952–60.
78. Ji J, Lu Y, Liu H, *et al*. Acupuncture and moxibustion for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med* 2013;**2013**:158352.
79. Lee DH, Kim JI, Lee MS, Choi TY, Choi SM, Ernst E. Moxibustion for ulcerative colitis: a systematic review and meta-analysis. *BMC Gastroenterol* 2010;**10**:36.
80. Scholmerich J: Trichuris suis ova in inflammatory bowel disease. *Dig Dis* 2013;**31**:391–5.
81. Ng SC, Lam YT, Tsoi KK, Chan FK, Sung JJ, Wu JC. Systematic review: the efficacy of herbal therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;**38**:854–63.
82. Rahimi R, Nikfar S, Abdollahi M. Induction of clinical response and remission of inflammatory bowel disease by use of herbal medicines: a meta-analysis. *World J Gastroenterol* 2013;**19**:5738–49.
83. Asakura H, Suzuki K, Kitahora T, Morizane T. Is there a link between food and intestinal microbes and the occurrence of Crohn's disease and ulcerative colitis? *J Gastroenterol Hepatol* 2008;**23**:1794–801.
84. Kucharzik T, Maaser C, Lugering A, *et al*. Recent understanding of IBD pathogenesis: implications for future therapies. *Inflamm Bowel Dis* 2006;**12**:1068–83.
85. Sartor RB. Probiotic therapy of intestinal inflammation and infections. *Curr Opin Gastroenterol* 2005;**21**:44–50.