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Herbal medicines for the treatment of inflammatory bowel disease (Protocol)

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[Intervention Protocol]

Herbal medicines for the treatment of inflammatory bowel disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objectives are to assess the efficacy and safety of herbal medicines for the treatment of patients with IBD.

BACKGROUND

Description of the condition

The term 'Inflammatory bowel disease' (IBD) describes a group of inflammatory conditions affecting the colon and small intestine (Langhorst 2005; Schmidt 2005; Xavier 2007). The most common conditions are Crohn's disease (CD) and ulcerative colitis (UC) (Xavier 2007). Although CD and UC differ, they may present with similar symptoms, including abdominal pain, diarrhoea, rectal bleeding and weight loss (Xavier 2007). Extraintestinal symptoms, such as anaemia and conditions due to malnutrition, are highly prevalent in patients suffering from IBD (Stein 2010). A diagnosis of UC or CD is based on the defining symptoms (rectal bleeding, diarrhoea, abdominal pain), and verified by colonoscopy and histopathology. Colonoscopy and the biopsy of pathological lesions are required to confirm the presence of inflammation in the intestine. The existence of inflammatory markers in patients' stool and blood samples also aid diagnosis and follow-up.

Despite considerable research effort, the etiology and pathophysiology of both UC and CD remain largely unknown (Khor 2011; Xavier 2007). Both conditions appear to be caused by multifactorial processes, relating to individuals' genetic predisposition, issues of immune dysregulation, barrier dysfunction and altered microbial flora (Asakura 2007; Khor 2011; Kucharzik 2006; Xavier 2007; Kucharzik 2006).

In addition to physical symptoms, IBD can cause psychological and social distress and reduces quality of life (Drossman 1989; Romberg-Camps 2010). Psychological factors have also been shown to influence the course of these diseases emphasizing the need for a multimodal therapy approach to treatment (Mawdsley 2005; Moradkhani 2013; Triantafillidis 2013).

Description of the intervention

Herbal medicine refers to the use of plants, plant components or preparations derived from them to cure or alleviate diseases, pathological conditions or functions of the body or mind (Bone 2013; Kraft 2010; Saller 2002). Herbal medicine is considered part of complementary and alternative medicine (CAM) as defined by the National Health Institute (NIH 2013). From this perspective, isolated active ingredients or synthetic derivatives from plants, are not considered to constitute herbal medicine (Saller 2002). Herbal medicines can take different forms, including the use of powders, teas, tablets, capsules, suppositories, extracts, lotions, fresh or dried plants (NIH 2013).

Herbal medicine has been used for thousands of years (Langhorst 2006); knowledge about the effects of medicinal plants having been passed down across the ages (Kraft 2010). The use of herbal medicine is also commonplace, both in traditional medicine and in home remedies. Most consumers assume that herbal medicine is safe (Heinrich 2012), natural and gentle; with the possibility of adverse effects being largely neglected (Ipsos MORI 2008). Adverse effects may occur, with direct toxic effects from biologically active constituents, or by contaminants and interactions between herbal and traditional medications (Bent 2008).

How the intervention might work

The intervention consists of a variety of herbal preparations, which may act through different mechanisms. Plants' cellular constituents include proteins, lipids or saccharides, intermediary metabolites such as organic acids and secondary cellular constituents such as alkaloids, glycosides, flavonoids, saponins, tannins and essential oils (Capasso 2003; Heinrich 2012). Whilst the exact composition of ingredients in particular herbal drugs remains unclear the secondary cellular constituents are generally assumed to be pharmacologically relevant (Capasso 2003). Such constituents may have anti-inflammatory, antiphlogistic or astringent properties, as well as exerting mucosal protective effects or even influencing fecal microflora. Most herbal medicines, however, act via the combination and interaction of all of their active ingredients (Heinrich 2012).

Herbal medications may also have psychological effects. Patients who use CAM therapies often report that they help them to gain a feeling of control over their diseases and treatments (Ipsos MORI 2008); perhaps thereby reducing their emotional distress and discomfort. A placebo effect may also contribute to CAM therapies' effectiveness.

Why it is important to do this review

The prevalence of CAM use in IBD patients ranges from 21 to 60% (Joos 2006; Joos 2011; Langhorst 2005; Li 2005; Weizmann 2012). Although a similar range of CAM therapies are used internationally, the use of single treatments differs widely between countries and regions (Hilsden 2011). Probiotics and fish oils are commonly used, with herbal medicines being used by 5 to 58% of IBD patients (Hilsden 2011). Most patients combine CAM with conventional medicine, rather than using it as an alternative treatment option. Patients prior beliefs and expectations are therefore likely to influence whether treatment effects are attributed to conventional or CAM treatment (Langhorst 2005). This may help to explain why surveys show that most patients treated with CAM do not report the amelioration of their symptoms (Fernández 2012). IBD patients' reasons for using CAM therapies are manifold. Many patients report serious adverse effects from conventional treatments (Weizmann 2012). Some patients seek to reduce their use of steroid medications (Langhorst 2005). Other patients see conventional therapies as ineffective (Hilsden 2011; Weizmann 2012), or they are searching for an optimum treatment (Langhorst 2005). Although most patients continue to use conventional medicine, once they start CAM therapy (Hilsden 2011), few appear to advise their treating physician of this fact (Ipsos MORI 2008), potentially causing adverse effects from interactions with prescription drugs.

While reviews and meta-analyses have been undertaken for probiotics (Mallon 2007; Naidoo 2011), and fish-oils (Turner 2007; Lev-Tzion 2014), high quality scientific evidence supporting the use of herbal medicine is lacking (Joos 2011). A systematic review evaluating the efficacy and safety of herbal medicines for the treatment of IBD is vital to provide reliable data to inform decision making by patients, physicians and CAM providers.

OBJECTIVES

The primary objectives are to assess the efficacy and safety of herbal medicines for the treatment of patients with IBD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials examining the effects of herbal medicines on IBD will be eligible for inclusion. Parallel group, crossover trials, and dose-finding studies will be considered for inclusion. Full text publications and abstract publications will be eligible for inclusion if sufficient information about study design, participants, interventions used and outcomes are reported.

Types of participants

Trials that include participants of both genders and any age, with active or quiescent UC or CD or both will be included. Data for patients with CD or UC will be analysed separately. No restriction on the diagnostic procedures or settings used in the studies will be applied. Studies that include participants with other disorders, such as irritable bowel syndrome, will be excluded.

Types of interventions

Any form of herbal medicine used for the management of IBD or IBD-related complaints, will be included, with the exception of traditional Chinese medicine herbal preparations which are covered by a Cochrane review (Gan 2009). For the purpose of this review, aroma therapy and homeopathy (mother tinctures only) preparations will be regarded as herbal medicines. Preparations of synthetic origin or those consisting only of plant derivatives will be excluded (Heinrich 2012; Kraft 2010; Saller 2002). Special emphasis will be paid to the quality of the herbal medicines used, and we will differentiate between studies that use herbal medicinal products or botanicals. In the studies using herbal medicinal products, the source of the therapeutic agents will be determined. Preparations produced in the European Union, Switzerland and Australia, will be differentiated from those produced elsewhere, as the former have high standards of quality regulation for the manufacture of herbal medicinal products, which the latter may not. No restrictions will be applied regarding control groups. Studies with placebo or no therapy controls, or any active control therapy will be eligible for inclusion as comparators. The use of concomitant medication or interventions will be allowed, if studies used them in both groups.

Types of outcome measures

Primary outcomes

The primary outcomes will be clinical remission or relapse (dichotomous outcomes) as defined by the included studiesClinical remission could be defined by several different clinical indices including the Colitis Activity Index (CAI score of $\leq$ 4), the Ulcerative Colitis - Disease Activity Index (UC-DAI score of $\leq$ 2), the Rachmilewitz index (score of $\leq$ 4), the Mayo score (score of $\leq$ 2), a Crohn's Disease Activity Index (CDAI score of < 150), or a Pediatric Crohn's Disease Activity Index (PCDAI score of $\leq$ 10 points).

Secondary outcomes

Secondary outcomes will include the following.

- Clinical response or improvement (dichotomous outcomes) as defined by the included studies. Clinical improvement could be defined by several different clinical indices. For example, a decrease of $\geq$ 70 points in the CDAI score from baseline, or a decrease of 30% or 3 points on the Mayo score.
- Clinical disease activity (continuous outcomes) as measured by various clinical indices. For example, the CDAI, PCDAI, the CAI, Mayo score, or Harry-Bradshaw Index or any other validated instrument.
- Endoscopic remission or improvement as defined by the included studies. Endoscopic remission or improvement could be defined by several different endoscopic indices. For example the Crohn's Disease Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Scale for Crohn's Disease (SES-CD) or the Rachmilewitz score or endoscopic index (EI), and endoscopic activity index (EAI) for patients with UC.
- Endoscopic relapse as defined by the included studies.
- Health-related quality of life as measured by any validated generic or disease-specific self-report scale such as the Short Form 36 Health Survey (SF-36), Short Form 12 Health Survey (SF-12), the Inflammatory Bowel Disease Questionnaire (IBDQ), and the EuroQol 5 Dimension Questionnaire (EQ-5D).
- Safety-related findings, for example reports of adverse events, serious adverse events, withdrawals due to adverse events or any abnormal laboratory findings.

Where more than one measure is used for an outcome in a reviewed study standard instruments will be preferred over novel ones and multi-item instruments over single-item ones.

Search methods for identification of studies

Electronic searches

The following databases will be searched from inception to date:
(a) MEDLINE (via OVID);
(b) EMBASE (via OVID);
(c) Scopus (via ScienceDirect);
(d) The Cochrane Library (CENTRAL);
(e) CAMBASE (www.cambase.de);
(f) AMED (Allied and Complementary Medicine Database, via OVID);
(g) The homeopathy research institute database (www.homeoinst.org/database); and
(h) The WHO International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx) for all registered and ongoing trials. This database also covers all entries from the Clinicaltrials.gov trial registry.
The search strategies to be used for each database are reported in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6 and Appendix 7.

Searching other resources

(a) Bibliographic screening.
We will check the reference lists of relevant trials or reviews to identify further trials. A copy of the full article for each reference reporting a potentially eligible trial will be obtained.
(b) Grey literature.
We will search the proceedings from the following congresses and annual meetings for relevant abstracts (from 2005 to date):

- International Congress on Complementary Medicine Research (ICCMR);
- European Congress for Integrative Medicine (ECIM);
- Digestive Disease Week (DDW);
- Annual Congress of the European Crohn's and Colitis Organisation (ECCO);
- United European Gastroenterology Week (UEGW); and
- Annual Scientific Meeting of the American College of Gastroenterology (ACG).

We will contact the Society for Medicinal Plant and Natural Product Research (GA), the Society for Phytotherapy (GPT) and the Committee for Research into Natural Medicine to identify trials on herbal medicine for patients with CD and UC.

Data collection and analysis

Selection of studies

Pairs of authors (RL/HC or RL/JL) will independently screen all of the study titles and abstracts identified from the literature search. Full papers of potentially eligible studies will then be read in full by the same authors to determine whether the studies concerned actually meet the review eligibility criteria. Disagreements will be discussed and resolved with a third author (PK). The study selection process will be documented using a PRISMA flow chart (Moher 2009). Excluded studies will be recorded in a 'Characteristics of excluded studies' table. No language restrictions will be applied. Studies in languages other than English, German, French, Russian, Chinese, Norwegian, Swedish or Islandic will be professionally translated.

Data extraction and management

Pairs of authors (RL/PK or RL/KK) will independently extract data from the included trials. We will enter the data in the 'Characteristics of included studies' table. All data will be checked for accuracy by a fourth author (HC). Disagreements will be discussed and resolved by agreement.
The following information will be extracted from the included studies:

- Methods: study design, methods of participant allocation, allocation concealment, blinding, drop-out rates and reasons for drop-out;
- Participants: country of origin, setting, sample size, diagnosis, diagnostic procedures, age, ethnicity;
- Intervention: type, dose, duration (for experimental and control interventions), quality of preparations used; and
- Outcomes: type of outcomes, assessment instruments used, assessment and follow-up intervals.

For trials with multiple publications, the earliest full journal publication will be considered the primary reference, however data will be extracted from all of the related publications as appropriate.

Assessment of risk of bias in included studies

Two authors (RL,PK) will independently assess study quality using the Cochrane risk of bias tool (Higgins 2011). The following domains will be assessed:

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting; and
- Other sources of bias.

Each domain will be judged as either:

- 'Low risk of bias' if the requirements are adequately fulfilled;
- 'High risk of bias' if the requirements are not adequately fulfilled; and
- 'Unclear risk of bias' if insufficient data for a judgement is provided.

Details of the requirements and rules for each judgement can be found in the Cochrane Handbook (Higgins 2011). The risk of bias assessment will provide the basis for a judgement of the quality of evidence provided, based on the GRADE recommendations (Brozek 2009; Guyatt 2008). We will use the GRADE approach, to assess the overall quality of evidence for the primary outcome and for selected secondary outcomes of interest. Outcomes from the pooling of randomized trials start as high quality evidence, but may be downgraded due to: (1) risk of bias, (2) indirectness (3) inconsistency (unexplained heterogeneity) (4) imprecision (sparse data) or (5) reporting bias (publication bias). We will use the GRADE profiler software to generate the GRADE analysis and summary of findings tables (GRADEpro).

Measures of treatment effect

We will calculate the risk ratio (RR) and corresponding 95% confidence interval (CI) for dichotomous outcomes. The primary outcomes, clinical remission and relapse will be classified as dichotomous outcomes (in remission versus not in remission or relapse).

A RR of > 1 for clinical remission, or a RR of < 1 for relapse will denote the superiority of the experimental treatment. We will calculate the mean difference (MD) and corresponding 95% CI for continuous outcomes. Clinical disease activity and health-related quality of life will be classified as continuous outcomes. When studies use different instruments to measure the same construct (e.g. SF-36 and IBDQ), we will calculate the standardized mean difference (SMD) and corresponding 95% CI. Post-interventional scores will be preferred over pre-post difference scores if available. A negative MD will be taken to indicate the beneficial effects of the experimental intervention over the control intervention for disease activity, while a positive MD will be taken to indicate the beneficial effects of the reviewed treatments for patients' quality of life. If the assessment instruments used are coded inversely, patients' scores will be inverted by multiplying them by -1. Safety outcomes will be classified as dichotomous (i.e. an adverse event versus no adverse event).

Unit of analysis issues

Studies of CD and UC, and those studies that enrolled patients with active or quiescent disease will be analysed separately. The effects of each herb or herbal preparation will also be considered separately.

In addition, studies with control groups using different types of interventions (e.g. placebo or active treatment) will be analysed separately and not combined in a single meta-analysis.

We will consider the following post-intervention measures if repeated outcome assessments are reported:

- For induction of remission studies the outcomes assessed closest to 8 weeks post-treatment, but not less than 4 or more than 16 weeks will be utilized for data analysis; and

- For maintenance of remission studies the outcomes assessed closest to 12 months, but not less than 6 months post-treatment will be utilized for data analysis.

Data from studies with non-standard designs will be handled according to the Cochrane Handbook (Higgins 2011). For crossover trials, paired data will be analysed. If these data are not available, then data from the first active interventional phase alone will be used. For studies presenting multiple, correlated comparisons, all relevant experimental intervention groups (e.g. groups using herbal preparations of varying doses) will be combined into a single group and all control intervention groups (e.g. groups with control medications of varying doses) will be combined into a single control group.

Dealing with missing data

Where data are missing, we will attempt to contact the study authors to obtain the missing data. If this approach fails, missing data will be imputed from existing scores, such as standard errors, confidence intervals or T-values as appropriate. Where neither of these approaches prove successful, average standard deviations, from other reviewed studies, using the same outcome measures, will be substituted for missing standard deviations. Sensitivity analyses will be conducted by excluding those studies where missing data had to be imputed (see below). The potential impact of missing data on the findings of the systematic review will be discussed.

Assessment of heterogeneity

Heterogeneity will be assessed using the Chi^2 test (Cochran 1954). A P value of ≤ 0.10 will be considered to indicate statistically significant heterogeneity. The magnitude of heterogeneity across studies will be assessed using the I^2 statistic (Higgins 2003). We will interpret the I^2 values as follows: 0 to 24% indicates low heterogeneity across studies; 25 to 49% indicates moderate heterogeneity across studies; 50 to 74% indicates substantial heterogeneity across studies; and 75 to 100% indicates considerable heterogeneity across studies.

Assessment of reporting biases

Publication bias will be assessed by funnel plots if ten or more studies are included in a meta-analysis. Funnel plots will be generated using the Review Manager 5 software (RevMan 2014). These plots will then be analysed visually. Generally symmetrical plots indicate a low risk of reporting bias, while asymmetrical ones indicate a high risk of such bias (Higgins 2011). However, other elements may also influence the symmetry of funnel plots.

Bias introduced by multiple publications will be addressed by including study results only once in a given analysis. If there is reasonable doubt that two publications report results from the same study attempts will be made to contact the trial authors to clarify the issue. Location bias will be addressed by searching multiple databases, including non-English language journals. Language bias will be avoided by including studies irrespective of the language of publication.

Data synthesis

Data will be pooled if at least two studies measure the same outcome in patients with the same disease, using the same intervention and control group. We will not pool data when the I^2 value is greater than 75%. We will calculate the pooled risk ratio and corresponding 95% CI for dichotomous outcomes using a random-effects model (inverse variance method, DerSimonian and Laird). We will calculate the pooled MD and corresponding 95% CI for continuous outcomes using a random-effects model. When studies use different instruments to measure the same construct (e.g. SF-36 and IBDQ), we will calculate the pooled SMD and

corresponding 95% CI. All analyses will be performed using the Review Manager 5 software (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

No subgroup analyses are planned. If statistical heterogeneity appears in any meta-analysis, sensitivity analyses will be used to explore possible reasons for this heterogeneity.

Sensitivity analysis

Studies with either inadequate random sequence generation or allocation concealment', a lack of blinding of the outcome assessors, or a high risk of attrition bias, will be excluded from analysis, to assess the robustness of point estimates. Further sensitivity analyses will be performed by excluding studies where missing data were imputed and studies that were unpublished or were published as abstracts only.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy for MEDLINE and EMBASE (via OVID)

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. exp Crohn disease/ or crohn*.mp.
22. (colitis and ulcerat*).mp.
23. ulcerative colitis.mp. or exp ulcerative colitis/
24. (inflammatory bowel disease* or IBD).mp.
25. extraintestinal.mp.
26. 21 or 22 or 23 or 24 or 25

27. 20 and 26
28. Phytotherapy.mp. or phytotherapy.tw.
29. (herbal or herb).tw.
30. (Plants or medicinal therapy).mp.
31. Botanicals.tw.
32. Anthroposophy.mp.
33. Anthroposoph*.tw.
34. Homeopathy.mp.
35. Homeopath*.tw.
36. Aromatherapy.mp.
37. Aromatherap*.tw.
38. (Frankincense or boswellia serrata).tw.
39. Curcumin.tw.
40. Wheat grass.tw.
41. Aloe vera.tw.
42. (Barley or hordeum vulgare).tw.
43. Remed*.tw.
44. (Marigold or calendula).tw.
45. Belladonna.tw.
46. (Ginger or zingiber officinale).tw.
47. Valerian*.tw.
48. (Licorice root or glycyrrhiza).tw.
49. (Indian plantago or plantago ovate).tw.
50. (Meadowsweet or filipendula ulmaria).tw.
51. (Turmeric or curcuma longa or curcuma xanthorriza).tw.
52. (Tormentil or potentilla erecta or tormentilla erecta or potentilla tormentilla).tw.
53. Myrrh.tw.
54. (Blackcurrant or ribes nigrum).tw.
55. (Blueberry or vaccinium myrtillus or bilberry).tw.
56. (Goldenseal or hydrastis Canadensis).tw.
57. (Ground ivy or glechoma hederacea).tw.
58. (Gentian or gentiana lutea).tw.
59. (Yarrow or achillea millefolium).tw.
60. (Peppermint or mentha piperita or mentha arvensis).tw.
61. (Oak bark or quercus).tw.
62. (Common alchemilla or Alchemilla arvensis).tw.
63. (Chinese rhubarb or Rheum officinale or Rheum palmatum).tw.
64. (Agrimony or Agrimonia eupatoria or Agrimonia officinalis).tw.
65. (Fumitory or Fumaria).tw.
66. Burdock root.tw.
67. (Wormwood or artemisia absinthium).tw.
68. (Dandelion root or taraxacum officinale).tw.
69. Artichoke.tw.
70. (Flaxseed or linseed).tw.
71. (Slippery elm or ulmus).tw.
72. Chamomile.tw. OR Matricaria.tw.
73. Tea.tw.
74. Herbal decoct*.tw.
75. or/28-74
76. 27 and 75

Appendix 2. Search strategy for Scopus (via ScienceDirect)

#1 TITLE-ABS-KEY (inflammatory bowel diseases)
#2 TITLE-ABS-KEY (colitis, ulcerative)
#3 TITLE-ABS-KEY (Crohn disease)
#4 **#1 OR #2 OR #3**
#5 TITLE-ABS-KEY (Phyto*)
#6 TITLE-ABS-KEY (herb*)
#7 TITLE-ABS-KEY (botanical)
#8 TITLE-ABS-KEY (Homeopath*)
#9 TITLE-ABS-KEY (plant)
#10 TITLE-ABS-KEY (Aromatherapy)
#11 TITLE-ABS-KEY (Frankincense) OR TITLE-ABS-KEY (boswellia serrata)
#12 TITLE-ABS-KEY (Curcumin)
#13 TITLE-ABS-KEY (Wheat grass)
#14 TITLE-ABS-KEY (Aloe vera)
#15 TITLE-ABS-KEY (Barley) OR TITLE-ABS-KEY (hordeum vulgare)
#16 TITLE-ABS-KEY (Marigold) OR TITLE-ABS-KEY (calendula)
#17 TITLE-ABS-KEY (Belladonna)
#18 TITLE-ABS-KEY (Ginger) OR TITLE-ABS-KEY (zingiber officinale)
#19 TITLE-ABS-KEY (Valerian)
#20 TITLE-ABS-KEY (Licorice root) OR TITLE-ABS-KEY (glycyrrhiza)
#21 TITLE-ABS-KEY (plantago)
#22 TITLE-ABS-KEY (Meadowsweet) OR TITLE-ABS-KEY (filipendula ulmaria
#23 TITLE-ABS-KEY (Turmeric) OR TITLE-ABS-KEY (curcuma)
#24 TITLE-ABS-KEY (Tormentil) OR TITLE-ABS-KEY (potentilla erecta) OR TITLE-ABS-KEY (tormentilla erecta) OR TITLE-ABS-KEY (potentilla tormentilla)
#25 TITLE-ABS-KEY (Myrrh)
#26 TITLE-ABS-KEY (Blackcurrant) OR TITLE-ABS-KEY (ribes nigrum)
#27 TITLE-ABS-KEY (Blueberry) OR TITLE-ABS-KEY (vaccinium myrtillus) OR TITLE-ABS-KEY (bilberry)
#28 TITLE-ABS-KEY (Goldenseal) OR TITLE-ABS-KEY (hydrastis canadensis)
#29 TITLE-ABS-KEY (Ground ivy) OR TITLE-ABS-KEY (glechoma hederacea)
#30 TITLE-ABS-KEY (Gentian) OR TITLE-ABS-KEY (gentiana lutea)
#31 TITLE-ABS-KEY (Yarrow) OR TITLE-ABS-KEY (achillea millefolium)
#32 TITLE-ABS-KEY (Peppermint) OR TITLE-ABS-KEY (mentha piperita) OR TITLE-ABS-KEY (mentha arvensis)
#33 TITLE-ABS-KEY (Oak bark) TITLE-ABS-KEY (quercus)
#34 TITLE-ABS-KEY (Common alchemilla) OR TITLE-ABS-KEY (Alchemilla arvensis)
#35 TITLE-ABS-KEY (Chinese rhubarb) OR TITLE-ABS-KEY (Rheum officinale) OR TITLE-ABS-KEY (Rheum palmatum)
#36 TITLE-ABS-KEY (Agrimony) OR TITLE-ABS-KEY (Agrimonia eupatoria) OR TITLE-ABS-KEY (Agrimonia officinalis)
#37 TITLE-ABS-KEY (Fumitory) OR TITLE-ABS-KEY (Fumaria)
#38 TITLE-ABS-KEY (Burdock root)
#39 TITLE-ABS-KEY (Wormwood) OR TITLE-ABS-KEY (artemisia absinthium)
#40 TITLE-ABS-KEY (Dandelion root) OR TITLE-ABS-KEY (taraxacum officinale)
#41 TITLE-ABS-KEY (Flaxseed) OR TITLE-ABS-KEY (linseed)
#42 TITLE-ABS-KEY (Slippery elm) OR TITLE-ABS-KEY (ulmus)
#43 TITLE-ABS-KEY (Chamomile) OR TITLE-ABS-KEY (Matricaria)
#44 TITLE-ABS-KEY (Artichoke)
#45 **#5 OR #6 OR … OR #44**
#46 TITLE-ABS (randomized controlled trial)
#47 TITLE-ABS (randomized)
#48 TITLE-ABS (randomly)
#49 TITLE-ABS (random)
#50 TITLE-ABS (trial)

#51 TITLE-ABS (groups)
#52 TITLE-ABS (placebo)
#53 TITLE-ABS (controlled)
#54 **#46 OR #47 OR … OR #53**
#55 **#4 AND #45 AND #54**
#56 **#7 AND #55**

Appendix 3. Search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#2 Ulcerative colitis
#3 Crohn disease
#4 **#1 OR #2 OR #3**
#5 MeSH descriptor: [Herbal therapy] explode all trees
#6 MeSH descriptor: [Homeopathy] explode all trees
#7**#5 OR #6**
#8 **#4 AND #7**

Appendix 4. Search strategy for CAMBASE

#1 Inflammatory Bowel Diseases
#2 ulcerative colitis
#3 Crohn disease
#4 **#1 OR #2 OR #3**

Appendix 5. Search strategy for AMED (via OVID)

#1 FT=Inflammatory bowel disease
#2 FT=ulcerative colitis
#3 FT=Crohn disease

Appendix 6. Search strategy for the homeopathy research institute database

#1 Inflammatory bowel disease
#2 ulcerative colitis
#3 Crohn disease
#4 **#1 OR #2 OR #3**

Appendix 7. Search strategy for the WHO International Clinical Trials Registry Platform

Advanced search:
1. Search terms:
2. Condition: Ulcerative colitis OR Crohn disease OR inflammatory bowel disease
Intervention: Phytotherapy OR herbal OR botanical OR homeopathy OR plant OR aromatherapy OR Frankincense OR boswellia OR Curcumin OR Wheat grass OR Aloe vera OR Barley OR Marigold OR calendula OR Belladonna OR Ginger OR zingiber officinale OR Valerian OR OR Licorice root OR glycyrrhiza OR plantago OR Meadowsweet OR filipendula ulmaria OR Turmeric OR curcuma OR Tormentil OR potentilla erecta OR tormentilla erecta OR potentilla tormentilla OR Myrrh OR Blackcurrant OR Blueberry OR vaccinium myrtillus OR bilberry OR Goldenseal OR hydrastis canadensis OR Ground ivy OR glechoma hederacea OR Gentian OR gentiana lutea OR Yarrow OR achillea millefolium OR Peppermint OR mentha piperita OR mentha arvensis OR Oak bark OR quercus OR Common alchemilla OR Alchemilla arvensis OR Chinese rhubarb OR Rheum officinale OR Rheum palmatum

OR Agrimony OR Agrimonia eupatoria OR Agrimonia officinalis OR Fumitory OR Fumaria OR Burdock root OR Wormwood OR artemisia absinthium OR Dandelion root OR taraxacum officinale OR Flaxseed OR linseed OR Slippery elm OR ulmus OR Chamomile OR Matricaria OR Artichoke OR supplement
Recruitment Status: ALL

CONTRIBUTIONS OF AUTHORS

1. Drafting the protocol: RL
2. Critically revising the protocol: HC, PK, KK, GD, JL
3. Run search: RL
4. Study selection: RL, HC, JL
5. Extract data from studies: RL, PK, KK
6. Enter data into RevMan: RL, PK
7. Carry out the analysis: RL, HC
8. Interpret the analysis: RL, HC, JL
9. Draft the final review: RL
10. Critically revising the final review: HC, PK, KK, GD, JL
11. Disagreement resolution: RL, PK, HC
12. Update the review: RL, HC, JL

DECLARATIONS OF INTEREST

None declared

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Internal sources

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