Study Protocol

Acupoint application therapy for diarrhea-predominant irritable bowel syndrome: a protocol for systematic review and network meta-analysis

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Background: Irritable bowel syndrome is a chronic functional gastrointestinal disease, of which diarrhea-predominant irritable bowel syndrome (IBS-D) is a common subtype. In China, acupoint application therapy is currently widely used as an effective complementary therapy for IBS-D. In the clinical management of IBS-D, acupoint application is usually combined with other therapies, including acupuncture, moxibustion, and Chinese herbal and Western medicine. However, at present, evidence regarding the most effective options for treating IBS-D is insufficient. Therefore, this protocol proposes a systematic review and network meta-analysis for evaluating the effectiveness of acupoint application and its combination therapies in treating IBS-D, and for identifying the acupoint application-related treatments with the highest probability of being the best intervention.

Methods: Six English electronic databases (PubMed, Ovid MEDLINE, Scopus, Web of Science, the Cochrane Library, and EMBASE), four Chinese electronic databases [China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CQVIP), WanFang, and SinoMed), and one Japanese medical database (Citation Information by National Institute of Informatics (CiNii)] will be searched for eligible randomized controlled trials from their inception to June 1, 2022. The efficacy and safety of acupoint application therapy and its combination therapies for patients with IBS-D will be evaluated. The STATA 14.0 (StataCorp, USA) software package will be used for the meta-analysis. A Bayesian network meta-analysis (NMA) will be performed using R (version 4.0.2) and Aggregate Data Drug Information System (ADDIS, version 1.16.8) software packages. Bias risk will be assessed using the Cochrane Collaboration's risk of bias tool; specifically, publication bias will be evaluated using Egger's test and funnel plots. The rank probabilities of various outcomes for each intervention will be calculated, clustered, and ranked using the cumulative ranking curve method. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method will be employed to assess the certainty of evidence for NMA outcomes.

Conclusions: This study will aim to determine the clinical efficacy of acupoint application therapy and its combined therapy in the treatment of IBS-D and provide an evidence-based foundation for identifying the best acupoint application program.

Keywords: Diarrhea-predominant irritable bowel syndrome (IBS-D); acupoint application therapy; network meta-analysis (NMA); systematic review

Submitted Jun 09, 2022. Accepted for publication Nov 10, 2022.
doi: 10.21037/apm-22-725
View this article at: https://dx.doi.org/10.21037/apm-22-725

Introduction

Irritable bowel syndrome (IBS) describes a common group of chronic functional gastrointestinal disorders characterized by recurrent episodes of abdominal pain, bloating, or abdominal discomfort with altered bowel habits (1). The global average prevalence of IBS is approximately 4.1% based on the Rome IV diagnostic criteria (2). According to the Bristol Stool Characterization Scale, IBS is usually classified into four subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS, mixed-type IBS, and unclassified IBS. Epidemiological surveys based on different diagnostic criteria have revealed variation in the prevalence of each subtype. Diarrhea-prominent IBS has a prevalence of 27.8% according to the Rome III criteria, while under the Rome IV criteria, it is the most common subtype, with a prevalence of 31.5% (3). Although IBS-D is not fatal, it seriously impacts quality of life, with patients often avoiding situations outside the home, which can lead to a loss of productivity at work or school. It can also affect patients' psychological health. Further, repeated medical visits due to IBS-D impose a burden on individual families and national healthcare services (4,5). Western medicine understands the pathogenesis of IBS to be influenced by a combination of genetics, psychosomatic factors, diet, infection, immunity, and other factors that lead to abnormal gut-brain interactions, which results in visceral hypersensitivity, abnormal gastrointestinal dynamics, and corresponding clinical symptoms (6). Commonly used drugs to treat IBS include smooth muscle antispasmodics, opioid receptor agonists/antagonists, bile acid sequestrants, and antidepressants (7). However, the pathophysiological mechanisms of IBS are still not fully understood; therefore, the efficacy of commonly prescribed Western drugs is limited. Moreover, the side effects of these drugs can lead to increased stress in patients. The first-line drugs for treating IBS-D, antispasmodics, for example, can bring about side effects such as fatigue, drowsiness, constipation, dizziness, and blurred vision (8). Therefore, there is a need to identify a treatment that offers better efficacy and safety than the current treatments for IBS-D.

In traditional Chinese medicine (TCM), IBS-D belongs to the categories of "diarrhea" and "abdominal pain". The disease location is considered to be the large intestine, and its onset is related to what is known in the TCM community as abnormalities of the spleen and liver functions. The main TCM treatment methods include herbal compounding, acupuncture, moxibustion, and acupoint application therapy (9-13). Among these, acupoint application is a specialized TCM therapy based on the theory of meridians and the theory of diagnosis and treatment in TCM that treats internal disease via an external application. Acupoint application combines the dual effects of acupoint stimulation and drug uptake, and its beneficial characteristics include simplicity, convenience, effectiveness, and being low cost (14). Further, acupoint application therapy is analogous to the transdermal drug delivery system. The drug is absorbed through the skin into the bloodstream, resulting in a relatively stable blood concentration and a longer-lasting effect while avoiding the first-pass effect in the gastrointestinal tract. Therefore, acupoint application does not share the disadvantages of internal drug administration, as a method that is widely applied by clinicians, which include damage to the spleen and stomach (15-17).

Recently, Dai *et al.* (18) conducted a network meta-analysis (NMA) to evaluate nonpharmacological interventions for IBS. By comparing its efficacy and safety with those of five other nonpharmacological interventions (moxibustion, biofeedback therapy, dietary regulation, cognitive behavioral therapy, and probiotics-based treatment), the authors found that acupuncture performed best in improving clinical efficacy and avoiding adverse effects. This finding suggests that acupoint therapy in which the needle pierces the patient's skin may be a potentially effective treatment for IBS. However, there is a lack of strong evidence regarding the efficacy and safety of acupoint application therapy in patients with IBS-D, and the appropriate choices of acupuncture points and Chinese herbs for IBS-D treatment still need clarification. For this reason, we have developed a protocol for a systematic review and NMA to compare the effects of different acupoint application therapies and combination therapies in IBS-D prevention and treatment, and to summarize the data regarding the frequency and association of acupoint treatment and drugs to inform clinical decision-making.

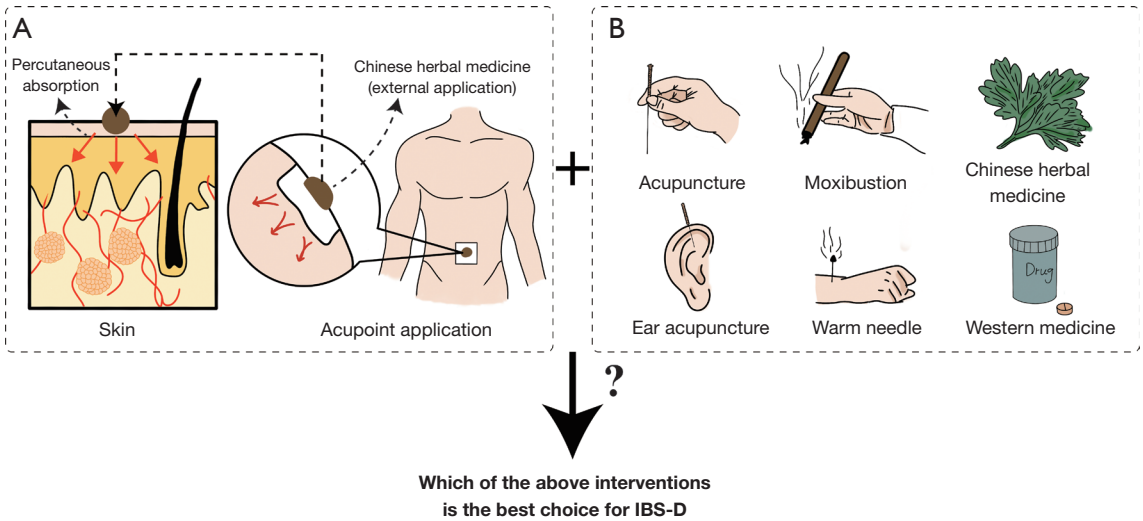

Figure 1 The research idea of acupoint application combined with other therapies for treating IBS-D. (A) Schematic illustration of acupoint application therapy (right) and percutaneous absorption of Chinese herbal medicine (left); (B) acupoint application therapy is usually combined with other therapies, including acupuncture, moxibustion, ear acupuncture, warm needle, and Chinese herbal and Western medicine. IBS-D, diarrhea-predominant irritable bowel syndrome.

The research idea is shown in *Figure 1*. We present the following article in accordance with the PRISMA-P reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-725/rc).

Methods

Protocol registration

The NMA has been registered on the Open Science Framework website (Review registry unique identifying DOI number: 10.17605/OSF.IO/XHUVA). All steps of the NMA conform with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for NMA guidelines (19). If any information adjustments are required during the entire study period, we will promptly correct and update the information before submitting the final report.

Ethics and dissemination

Since this protocol does not include patient recruitment or the collection of personal information about medical personnel or patients, this study does not require ethical approval. There are no ethical concerns, and informed consent is not required.

Eligibility criteria

Type of study

Randomized controlled trials (RCTs) that evaluated the efficacy and adverse effects of acupoint application therapy or its combination with other therapies for the treatment of IBS-D will be included in this study. The review will cover studies in multiple languages.

Participants

Patients must have been diagnosed with IBS-D in accordance with clear diagnostic criteria (20,21), and there will be no restrictions according to sex, age, or disease stage. Diagnoses meeting any of the Rome criteria will be considered sufficient.

Interventions

In the treatment group, the interventions will include simple acupoint application therapy and combined acupoint application therapy with other medical treatments, such as acupuncture, moxibustion, massage, physiotherapy, Chinese herbal compound prescription, or Western medicine. The range of acupoints selected or drugs used will not be restricted.

The intervention in the control group will be a placebo.

Outcomes

Studies reporting on the following outcome indicators will be included in the meta-analysis.

(I) Evaluation indicators reflecting overall efficacy: the IBS symptom severity scale (IBS-SSS), IBS adequate relief (IBS-AR), IBS satisfactory relief (IBS-SR), the IBS Global Improvement Scale (IBS-GIS), the Spleen and Stomach Disease PRO (patient-reported outcomes) scale, the total effective rate of clinical symptoms, or TCM symptom therapeutic effect evaluation.

(II) Evaluation indicators reflecting the degree of improvement in clinical symptoms: the gastrointestinal symptom rating scale for IBS (GSRS-IBS), the visual analog scale (VAS), the Bristol Stool Form Scale, defecation satisfaction, defecation frequency, or other evaluation indexes for gastrointestinal symptoms.

(III) Evaluation indicators reflecting the patient's quality of life: the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), IBS Quality of Life instrument (IBS-QoL), IBS impact scale (IBS-IS), or Work and Social Adjustment Scale (WSAS).

(IV) Evaluation indicators reflecting the patient's psychological status: the Zung Self-Rating Anxiety Scale (SAS), the Zung Self-Rating Depression Scale (SDS), the Hamilton Anxiety Scale (HAMA), or the Hamilton Depression Scale (HAMD).

(V) Evaluation indicators reflecting the long-term efficacy and safety of the treatment: long-term efficacy assessed in terms of the relapse rate and follow-up, and safety assessed by the number of adverse reactions that occurred, including the total number of adverse reactions, trial-related adverse reactions (e.g., a rash or diarrhea), and other unrelated adverse reactions for which patients were withdrawn from the trial.

Exclusion criteria

In the selection of studies for the meta-analysis, the following exclusions will apply.

(I) For repeated publications, only literatures containing complete, original data will be retained; the rest will be excluded.

(II) Literatures containing only abstract data while lacking specific data and relevant indicators will be automatically excluded from the review. No effort will be made to contact the relevant authors directly, as such an investigative approach would bypass the formal academic peer review process.

(III) Non-RCT studies, such as case reports, experience summaries, and animal research, will be excluded.

(IV) Studies with unclear diagnostic criteria and outcome indicators will be excluded.

(V) Studies lacking sufficient information on selected acupoints and Chinese herbs will be excluded.

Search strategy

Two researchers will independently conduct searches for all RCTs relating to acupoint application for IBS-D published in 11 databases from the date of their inception to June 1, 2022. The 11 databases are PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Scopus database (http://www.scopus.com/), Web of Science (http://www.webofscience.com), Ovid MEDLINE (http://www.ovid.com/site/index.jsp), the Cochrane Library (http://www.cochranelibrary.com/), EMBASE (http://www.embase.com/), SinoMed (http://www.sinomed.ac.cn/), CNKI (China National Knowledge Infrastructure, http://www.cnki.net/), CQVIP (China Science and Technology Journal Database, http://www.cqvip.com/), Wanfang Data Knowledge Service Platform (http://www.wanfangdata.com.cn/index.html), and CiNii (Citation Information by National Institute of Informatics, https://ci.nii.ac.jp/CiNii). Also, links to further relevant literatures will be traced and followed up. The results of each database will be checked at the end of the independent searches to ensure completeness.

The searches will be conducted using a combination of subject terms and individual words. The search terms will include disease names, such as "irritable bowel syndrome", "diarrhea-predominant irritable bowel syndrome", "IBS-D", "irritable bowel", "irritable colon", "functional diarrhea", "diarrhea", "functional gastrointestinal disorders", "disorders of gut-brain interaction", and "functional colonic diseases". Keywords relating to treatment measures will include "acupoint application", "acupoint sticking", "acupuncture point paste", "herbal patch", "herbal plaster", "belly button patch", "traditional Chinese medicine patch", "transdermal patch", "cutaneous administration", and "external application". The search terms will be adapted appropriately to conform to the different syntactic rules of the 11 databases. As an example, the retrieval strategy for

Table 1 The search strategy for the PubMed database

Number	Search term
#1	Irritable Bowel Syndrome [MeSH]
#2	Colonic Diseases, Functional [MeSH]
#3	irritable bowel syndrome [Title/Abstract]
#4	functional colonic diseases [Title/Abstract]
#5	diarrhea-predominant irritable bowel syndrome [Title/Abstract]
#6	IBS-D [Title/Abstract]
#7	irritable bowel [Title/Abstract]
#8	irritable colon [Title/Abstract]
#9	functional diarrhea [Title/Abstract]
#10	diarrhea [Title/Abstract]
#11	functional gastrointestinal disorder [Title/Abstract]
#12	functional gastrointestinal disorders [Title/Abstract]
#13	FGID [Title/Abstract]
#14	disorder of gut-brain interaction [Title/Abstract]
#15	disorders of gut-brain interaction [Title/Abstract]
#16	DGBI [Title/Abstract]
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	Administration, Cutaneous [MeSH]
#19	Transdermal Patch [MeSH]
#20	cutaneous administration [Title/Abstract]
#21	transdermal patch [Title/Abstract]
#22	acupoint application [Title/Abstract]
#23	acupoints application [Title/Abstract]
#24	acupoint sticking [Title/Abstract]
#25	acupoints sticking [Title/Abstract]
#26	acupuncture point paste [Title/Abstract]
#27	herb patching [Title/Abstract]
#28	herbal patching [Title/Abstract]
#29	herb plaster [Title/Abstract]
#30	herbal plaster [Title/Abstract]
#31	belly button patch [Title/Abstract]
#32	belly button patching [Title/Abstract]
#33	Chinese medicine application [Title/Abstract]
#34	traditional Chinese medicine patch [Title/Abstract]
#35	external application [Title/Abstract]
#36	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37	#17 AND #36

IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

PubMed is shown in *Table 1*. The retrieval strategies for all databases are shown in Tables S1-S11.

Data screening and extraction

The relevant literature in the selected databases will be screened by the two researchers independently. In the event of disagreements during cross-checking, a third researcher will be consulted to reach a group decision. Initial screening will be carried out according to titles and abstracts, at which point, duplicate and irrelevant studies will be eliminated. Re-screening will be carried out by reading the full texts and then culling unsuitable literature in line with the inclusion and exclusion criteria. The literature screening process is shown in *Figure 2*.

The data extracted from the studies will cover four main domains: (I) general information of the authors (the first author's name, year of publication, country or region of study); (II) baseline information of the treatment and control groups (diagnostic criteria, sample size, sex, duration of disease); (III) interventions (acupoints, Chinese herbs, duration of treatment, follow-up time); and (IV) outcome indicators (the overall efficacy of IBS-D-related diseases, major clinical symptoms, quality of life, psychological status, safety and evaluation indicators of long-term efficacy).

Literature quality assessment

The Cochrane Handbook 5.1.0 method (22) will be used to assess the risk of bias. The following seven aspects will be independently assessed by two researchers: selection bias, performance bias, attrition bias, reporting bias, and other kinds of bias. The risk of bias will be assessed as "low risk", "high risk", or "unclear". Publication bias will be evaluated

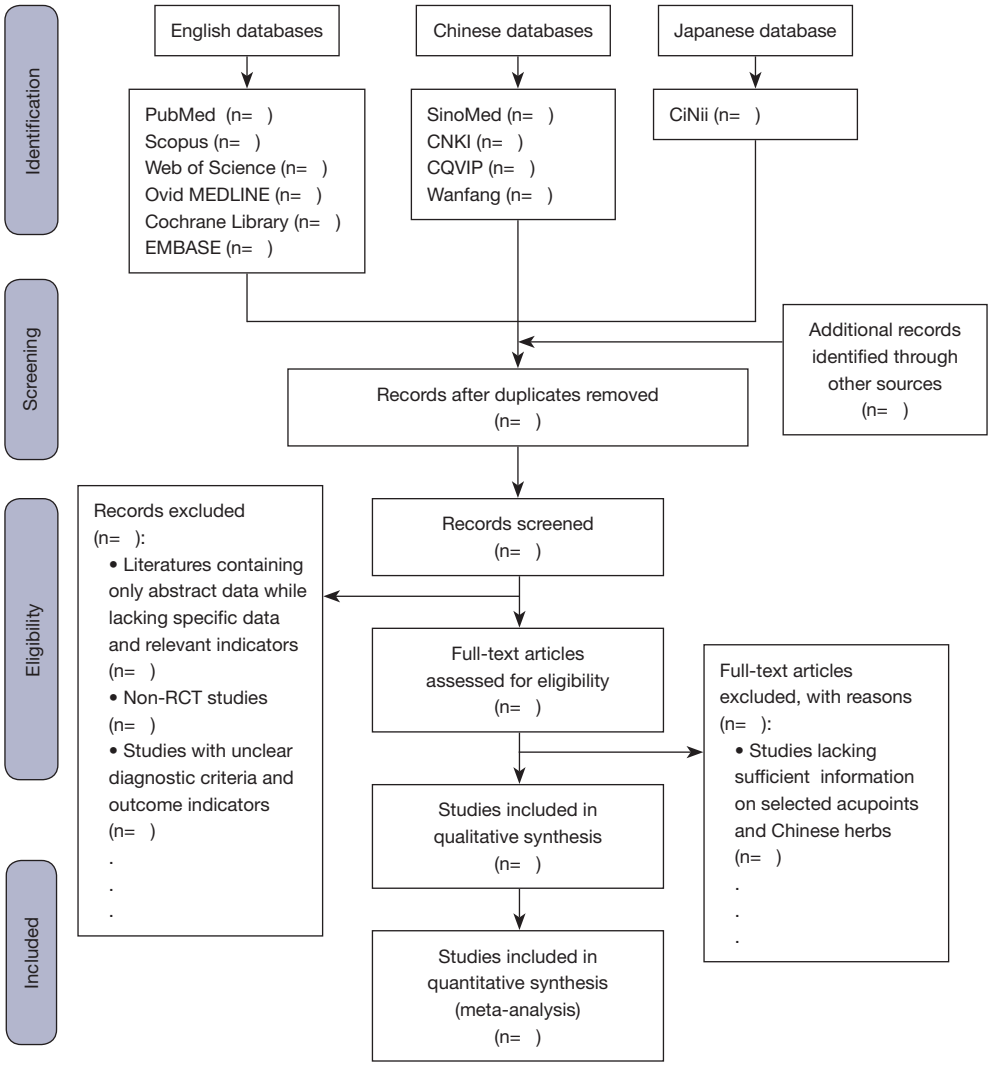

Figure 2 Flow diagram of the overview of the network meta-analysis. CNKI, China National Knowledge Infrastructure; CQVIP, China Science and Technology Journal Database; CiNii, Citation Information by National Institute of Informatics; RCT, randomized controlled trial.

using Egger's test and funnel plots.

Statistical analysis

Traditional meta-analysis (23) will be performed using STATA version 14.0 (STATA Corp., College Station, TX). Odds ratios (OR) and 95% confidence intervals (CI) will serve as the dichotomous variable effect statistical instruments, and mean difference (MD) and 95% CI will serve as the continuous variable effect statistical instruments. Should any of these units of measurement be found to yield unsatisfactory results, the standardized mean difference (SMD) method will be used. Heterogeneity between study data will be analyzed using the chi-squared test, with an I^2 statistic of 25–49%, 50–74%, and ≥75% considered low, medium, and high levels of heterogeneity, respectively. If I^2 is ≤0% or P>0.05, the meta-analysis will be performed using a fixed-effects model; otherwise, the source of heterogeneity will need to be further explored, and a random-effects model will be used for the meta-analysis (24).

The NMA (25) will be performed using R version 4.0.2 (College Station, TX, USA), Stata version 14.0, and ADDIS version 1.16.8 (Drugis, Groningen, NL, https://addis.drugis.org) statistical software-related packages. Using R version 4.0.2, the code for the Bayesian Markov chain-Monte Carlo algorithm will be entered to perform

the network analysis and plot the results of the random-effects model. In Aggregate Data Drug Information System (ADDIS, version 1.16.8), with the initial value set to 2.5, four chains will be simulated with an iteration step size of 10, whereby the number of iterations will initially be set to 20,000. In total, 50,000 iterations will be simulated for a priori evaluation and processing (26), and the difference will be considered statistically significant at $P<0.05$. Inconsistency will be tested for using the node-split model. When $P>0.05$, the selected studies will be considered to be heterogeneous, and the consistency model will be used for analysis; otherwise, the inconsistency model will be applied (27). Convergence will be measured using the potential scale reduction factor method. A result close to or equal to 1 will be taken to indicate good convergence and that the results from the inconsistency model analysis are reliable (28). To identify the acupoint application-related therapy with the highest probability of being the best intervention, individual interventions will be ranked using a hierarchical probability ranking diagram.

If significant clinical heterogeneity is observed in the combined effect sizes, further subgroup analyses or sensitivity analyses will be performed. If more than ten trials are included in the study, funnel plots and Egger's test will be used to determine whether publication bias is present. Frequency, hierarchical clustering, association rules, and complex network analyses will be used to identify the best practicable laws of acupoint and TCM. These tests will be run in R version 4.0.2 and SPSS version 24.0 (SPSS Inc., Chicago, Illinois, USA).

Evidence quality evaluation

The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, using which evidence is graded as A (high quality), B (moderate quality), C (low quality), or D (very low quality). After screening, the quality of evidence in the selected studies will be assessed for at least five outcome indicators (29).

Discussion

Acupoint application therapy is a form of medical treatment that acts locally and systemically. Acupoint application is prepared by first crushing herbs or pounding them to extract juices and active ingredients, and then adding honey, ginger juice, petroleum jelly, and other excipients to prepare a dosage that is applied to particular acupuncture points. Acupoint application therapy has been practiced in China for more than 2,000 years and is currently widely used to treat chronic pain and chronic diseases of the respiratory and digestive systems (30). Summaries of evidence have been published on the use of acupoint application therapy in the treatment of chronic obstructive pulmonary disease (31), bronchitis (32), allergic rhinitis (33), anorexia nervosa (34), essential hypertension (35), primary dysmenorrhea (36), and acute gouty arthritis (37,38). However, at present, the existing body of systematic reviews regarding the efficacy and safety of this therapy for IBS-D is limited. Therefore, we will conduct a systematic review and meta-analysis to assess the efficacy and safety of acupoint application therapy, and to summarize the frequency and optimal combination of acupoints and Chinese herbs. It is hoped that the study results will serve as a benchmark for developing appropriate acupoint application therapy regimens.

Acknowledgments

The authors acknowledge the OSF system for providing us with a platform to register this study protocol. We sincerely thank C. Mullens, J. Reynolds (from AME Publishing Company), and M. Sutherland (from University of Glasgow) for providing English language editing support with this protocol.

Funding: This research will be supported by funding from the Scientific Research Project of the Second Clinical Medical College of Guangzhou University of Traditional Chinese Medicine (No. 2018002 to Shaowei Li).

Footnote

Reporting Checklist: The authors have completed the PRISMA-P reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-725/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-725/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-725/coif). SL reports that this research will be supported by funding from the Scientific Research Project of the Second Clinical Medical College of Guangzhou University of Traditional Chinese Medicine (No. 2018002). The other authors have

no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Since this protocol does not include patient recruitment or the collection of personal information about medical personnel or patients, this study does not require ethical approval. There are no ethical concerns, and informed consent is not required.

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Cite this article as: Yin X, Li S, Ouyang M, Ou R, Chen Z, Wei S, Huang H, Liu D. Acupoint application therapy for diarrhea-predominant irritable bowel syndrome: a protocol for systematic review and network meta-analysis. Ann Palliat Med 2022;11(12):3785-3793. doi: 10.21037/apm-22-725

Supplementary

Table S1 The search strategy for the PubMed database

Number	Search term
#1	Irritable Bowel Syndrome [MeSH]
#2	Colonic Diseases, Functional [MeSH]
#3	irritable bowel syndrome [Title/Abstract]
#4	functional colonic diseases [Title/Abstract]
#5	diarrhea-predominant irritable bowel syndrome [Title/Abstract]
#6	IBS-D [Title/Abstract]
#7	irritable bowel [Title/Abstract]
#8	irritable colon [Title/Abstract]
#9	functional diarrhea [Title/Abstract]
#10	diarrhea [Title/Abstract]
#11	functional gastrointestinal disorder [Title/Abstract]
#12	functional gastrointestinal disorders [Title/Abstract]
#13	FGID [Title/Abstract]
#14	disorder of gut-brain interaction [Title/Abstract]
#15	disorders of gut-brain interaction [Title/Abstract]
#16	DGBI [Title/Abstract]
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	Administration, Cutaneous [MeSH]
#19	Transdermal Patch [MeSH]
#20	cutaneous administration [Title/Abstract]
#21	transdermal patch [Title/Abstract]
#22	acupoint application [Title/Abstract]
#23	acupoints application [Title/Abstract]
#24	acupoint sticking [Title/Abstract]
#25	acupoints sticking [Title/Abstract]
#26	acupuncture point paste [Title/Abstract]
#27	herb patching [Title/Abstract]
#28	herbal patching [Title/Abstract]
#29	herb plaster [Title/Abstract]
#30	herbal plaster [Title/Abstract]
#31	belly button patch [Title/Abstract]
#32	belly button patching [Title/Abstract]
#33	Chinese medicine application [Title/Abstract]
#34	traditional Chinese medicine patch [Title/Abstract]
#35	external application [Title/Abstract]
#36	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37	#17 AND #36

IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

https://dx.doi.org/10.21037/apm-22-725

Table S2 The search strategy for the Ovid Medline database

Number	Search term
#1	irritable bowel syndrome.af.
#2	IBS.af.
#3	diarrhea-predominant irritable bowel syndrome.af.
#4	IBS-D.af.
#5	functional colonic diseases.af.
#6	irritable bowel.af.
#7	irritable colon.af.
#8	functional diarrhea.af.
#9	diarrhea.af.
#10	functional gastrointestinal disorder.af.
#11	functional gastrointestinal disorders.af.
#12	FGID.af.
#13	disorder of gut-brain interaction.af.
#14	disorders of gut-brain interaction.af.
#15	DGBI.af.
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	cutaneous administration.af.
#18	transdermal patch.af.
#19	acupoint application.af.
#20	acupoints application.af.
#21	acupoint sticking.af.
#22	acupoints sticking.af.
#23	acupuncture point paste.af.
#24	herb patching.af.
#25	herbal patching.af.
#26	herb plaster.af.
#27	herbal plaster.af.
#28	belly button patch.af.
#29	belly button patching.af.
#30	Chinese medicine application.af.
#31	traditional Chinese medicine patch.af.
#32	external application.af.
#33	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#16 AND #33

IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

https://dx.doi.org/10.21037/apm-22-725

Table S3 The search strategy for the Scopus database

Number	Search term
#1	TITLE-ABS-KEY(irritable bowel syndrome)
#2	TITLE-ABS-KEY(IBS)
#3	TITLE-ABS-KEY (diarrhea-predominant irritable bowel syndrome)
#4	TITLE-ABS-KEY (IBS-D)
#5	TITLE-ABS-KEY (functional colonic diseases)
#6	TITLE-ABS-KEY (irritable bowel)
#7	TITLE-ABS-KEY (irritable colon)
#8	TITLE-ABS-KEY (functional diarrhea)
#9	TITLE-ABS-KEY (diarrhea)
#10	TITLE-ABS-KEY (functional gastrointestinal disorder)
#11	TITLE-ABS-KEY (functional gastrointestinal disorders)
#12	TITLE-ABS-KEY (FGID)
#13	TITLE-ABS-KEY (disorder of gut-brain interaction)
#14	TITLE-ABS-KEY (disorders of gut-brain interaction)
#15	TITLE-ABS-KEY DGBI (Topic)
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	TITLE-ABS-KEY (cutaneous administration)
#18	TITLE-ABS-KEY (transdermal patch)
#19	TITLE-ABS-KEY (acupoint application)
#20	TITLE-ABS-KEY (acupoints application)
#21	TITLE-ABS-KEY (acupoint sticking)
#22	TITLE-ABS-KEY (acupoints sticking)
#23	TITLE-ABS-KEY (acupuncture point paste)
#24	TITLE-ABS-KEY (herb patching)
#25	TITLE-ABS-KEY (herbal patching)
#26	TITLE-ABS-KEY (herb plaster)
#27	TITLE-ABS-KEY (herbal plaster)
#28	TITLE-ABS-KEY (belly button patch)
#29	TITLE-ABS-KEY (belly button patching)
#30	TITLE-ABS-KEY (Chinese medicine application)
#31	TITLE-ABS-KEY (traditional Chinese medicine patch)
#32	TITLE-ABS-KEY (external application)
#33	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#16 AND #33

IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

https://dx.doi.org/10.21037/apm-22-725

Table S4 The search strategy for the Web of Science database

Number	Search term
#1	irritable bowel syndrome (Topic)
#2	IBS (Topic)
#3	diarrhea-predominant irritable bowel syndrome (Topic)
#4	IBS-D (Topic)
#5	functional colonic diseases (Topic)
#6	irritable bowel (Topic)
#7	irritable colon (Topic)
#8	functional diarrhea (Topic)
#9	diarrhea (Topic)
#10	functional gastrointestinal disorder (Topic)
#11	functional gastrointestinal disorders (Topic)
#12	FGID (Topic)
#13	disorder of gut-brain interaction (Topic)
#14	disorders of gut-brain interaction (Topic)
#15	DGBI (Topic)
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	cutaneous administration (Topic)
#18	transdermal patch (Topic)
#19	acupoint application (Topic)
#20	acupoints application (Topic)
#21	acupoint sticking (Topic)
#22	acupoints sticking (Topic)
#23	acupuncture point paste (Topic)
#24	herb patching (Topic)
#25	herbal patching (Topic)
#26	herb plaster (Topic)
#27	herbal plaster (Topic)
#28	belly button patch (Topic)
#29	belly button patching (Topic)
#30	Chinese medicine application (Topic)
#31	traditional Chinese medicine patch (Topic)
#32	external application (Topic)
#33	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#16 AND #33

IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

https://dx.doi.org/10.21037/apm-22-725

Table S5 The search strategy for the Cochrane Library database

Number	Search term
#1	MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
#2	MeSH descriptor: [Colonic Diseases, Functional] explode all trees
#3	(irritable bowel syndrome):ti,ab,kw
#4	(functional colonic diseases):ti,ab,kw
#5	(diarrhea-predominant irritable bowel syndrome):ti,ab,kw
#6	(IBS-D):ti,ab,kw
#7	(irritable bowel):ti,ab,kw
#8	(irritable colon):ti,ab,kw
#9	(functional diarrhea):ti,ab,kw
#10	(diarrhea):ti,ab,kw
#11	(functional gastrointestinal disorder):ti,ab,kw
#12	(functional gastrointestinal disorders):ti,ab,kw
#13	(FGID):ti,ab,kw
#14	(disorder of gut-brain interaction):ti,ab,kw
#15	(disorders of gut-brain interaction):ti,ab,kw
#16	(DGBI):ti,ab,kw
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	MeSH descriptor: [Administration, Cutaneous] explode all trees
#19	MeSH descriptor: [Transdermal Patch] explode all trees
#20	(cutaneous administration):ti,ab,kw
#21	(transdermal patch):ti,ab,kw
#22	(acupoint application):ti,ab,kw
#23	(acupoints application):ti,ab,kw
#24	(acupoint sticking):ti,ab,kw
#25	(acupoints sticking):ti,ab,kw
#26	(acupuncture point):ti,ab,kw
#27	(herb patching):ti,ab,kw
#28	(herbal patching):ti,ab,kw
#29	(herb plaster):ti,ab,kw
#30	(herbal plaster):ti,ab,kw
#31	(belly button patch):ti,ab,kw
#32	(belly button patching):ti,ab,kw
#33	(Chinese medicine application):ti,ab,kw
#34	(traditional Chinese medicine patch):ti,ab,kw
#35	(external application):ti,ab,kw
#36	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37	#17 AND #36

IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

https://dx.doi.org/10.21037/apm-22-725

Table S6 The search strategy for the EMBASE database

Number	Search term
#1	irritable bowel syndrome:ab,kw,ti
#2	IBS:ab,kw,ti
#3	diarrhea-predominant irritable bowel syndrome:ab,kw,ti
#4	IBS-D:ab,kw,ti
#5	functional colonic diseases:ab,kw,ti
#6	irritable bowel:ab,kw,ti
#7	irritable colon:ab,kw,ti
#8	functional diarrhea:ab,kw,ti
#9	diarrhea:ab,kw,ti
#10	functional gastrointestinal disorder:ab,kw,ti
#11	functional gastrointestinal disorders:ab,kw,ti
#12	FGID:ab,kw,ti
#13	disorder of gut-brain interaction:ab,kw,ti
#14	disorders of gut-brain interaction:ab,kw,ti
#15	DGBI:ab,kw,ti
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	cutaneous administration:ab,kw,ti
#18	transdermal patch:ab,kw,ti
#19	acupoint application:ab,kw,ti
#20	acupoints application:ab,kw,ti
#21	acupoint sticking:ab,kw,ti
#22	acupoints sticking:ab,kw,ti
#23	acupuncture point paste:ab,kw,ti
#24	herb patching:ab,kw,ti
#25	herbal patching:ab,kw,ti
#26	herb plaster:ab,kw,ti
#27	herbal plaster:ab,kw,ti
#28	belly button patch:ab,kw,ti
#29	belly button patching:ab,kw,ti
#30	Chinese medicine application:ab,kw,ti
#31	traditional Chinese medicine patch:ab,kw,ti
#32	external application:ab,kw,ti
#33	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#16 AND #33

IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction.

https://dx.doi.org/10.21037/apm-22-725

Table S7 The search strategy for the CNKI database

编号	检索词
#1	主题检索'SU：”穴位敷贴”
#2	主题检索'SU：”敷贴”
#3	主题检索'SU：”穴位贴敷”
#4	主题检索'SU：”贴敷”
#5	主题检索'SU：”穴位贴”
#6	主题检索'SU：”经穴给药”
#7	主题检索'SU：”中药敷贴”
#8	主题检索'SU：”中药贴敷”
#9	主题检索'SU：”膏贴”
#10	主题检索'SU：”脐贴”
#11	主题检索'SU：”贴脐”
#12	主题检索'SU：”敷脐”
#13	主题检索'SU：”脐疗”
#14	主题检索'SU：”三伏贴”
#15	主题检索'SU：”伏九贴”
#16	主题检索'SU：”三九贴”
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	主题检索'SU：”腹泻型肠易激综合征”
#19	主题检索'SU：”腹泻型肠易激综合症”
#20	主题检索'SU：”腹泻型肠易激综合证”
#21	主题检索'SU：”IBS-D”
#22	主题检索'SU：”功能性腹泻”
#23	主题检索'SU：”功能性胃肠功能紊乱”
#24	主题检索'SU：”功能性胃肠疾病”
#25	主题检索'SU：”FGID”
#26	主题检索'SU：”结肠易激”
#27	主题检索'SU：”结肠功能紊乱”
#28	主题检索'SU：”肠脑轴”
#29	主题检索'SU：”肠 - 脑功能紊乱”
#30	主题检索'SU：”肠脑互动障碍”
#31	主题检索'SU：” DGBI “
#32	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33	主题检索'SU：”随机”
#34	主题检索'SU：”对照”
#35	主题检索'SU：”RCT”
#36	#33 OR #34 OR #35
#37	#17 AND #32 AND #36

IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction; RCT, randomized controlled trial.

https://dx.doi.org/10.21037/apm-22-725

Table S8 The search strategy for the CQVIP database

编号	检索词
#1	题名或关键词'M:（穴位敷贴）
#2	题名或关键词'M:（敷贴）
#3	题名或关键词'M:（穴位贴敷）
#4	题名或关键词'M:（贴敷）
#5	题名或关键词'M:（穴位贴）
#6	题名或关键词'M:（经穴给药）
#7	题名或关键词'M:（中药敷贴）
#8	题名或关键词'M:（中药贴敷）
#9	题名或关键词'M:（膏贴）
#10	题名或关键词'M:（脐贴）
#11	题名或关键词'M:（贴脐）
#12	题名或关键词'M:（敷脐）
#13	题名或关键词'M:（脐疗）
#14	题名或关键词'M:（三伏贴）
#15	题名或关键词'M:（伏九贴）
#16	题名或关键词'M:（三九贴）
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	题名或关键词'M:（腹泻型肠易激综合征）
#19	题名或关键词'M:（腹泻型肠易激综合症）
#20	题名或关键词'M:（腹泻型肠易激综合证）
#21	题名或关键词'M:(IBS-D)
#22	题名或关键词'M:（功能性腹泻）
#23	题名或关键词'M:（功能性胃肠功能紊乱）
#24	题名或关键词'M:（功能性胃肠疾病）
#25	题名或关键词'M:(FGID)
#26	题名或关键词'M:（结肠易激）
#27	题名或关键词'M:（结肠功能紊乱）
#28	题名或关键词'M:（肠脑轴）
#29	题名或关键词'M:（肠脑互动障碍）
#30	题名或关键词'M:（肠 - 脑功能紊乱）
#31	题名或关键词'M:(DGBI)
#32	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33	题名或关键词'M:（随机）
#34	题名或关键词'M:（对照）
#35	题名或关键词'M:(RCT)
#36	#33 OR #34 OR #35
#37	#17 AND #32 AND #36

IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction; RCT, randomized controlled trial.

https://dx.doi.org/10.21037/apm-22-725

Table S9 The search strategy for the WanFang database

编号	检索词
#1	主题检索：”穴位敷贴”
#2	主题检索：”敷贴”
#3	主题检索：”穴位贴敷”
#4	主题检索：”贴敷”
#5	主题检索：”穴位贴”
#6	主题检索：”经穴给药”
#7	主题检索：”中药敷贴”
#8	主题检索：”中药贴敷”
#9	主题检索：”膏贴”
#10	主题检索：”脐贴”
#11	主题检索：”贴脐”
#12	主题检索：”敷脐”
#13	主题检索：”脐疗”
#14	主题检索：”三伏贴”
#15	主题检索：”伏九贴”
#16	主题检索：”三九贴”
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	主题检索：”腹泻型肠易激综合征”
#19	主题检索：”腹泻型肠易激综合症”
#20	主题检索：”腹泻型肠易激综合证”
#21	主题检索：” IBS-D “
#22	主题检索：”功能性腹泻”
#23	主题检索：”功能性胃肠功能紊乱”
#24	主题检索：”功能性胃肠疾病”
#25	主题检索：” FGID “
#26	主题检索：”结肠易激”
#27	主题检索：”结肠功能紊乱”
#28	主题检索：”肠脑轴”
#29	主题检索：”肠脑互动障碍”
#30	主题检索：”肠 - 脑功能紊乱”
#31	主题检索：” DGBI”
#32	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33	主题检索：”随机”
#34	主题检索：”对照”
#35	主题检索：” RCT”
#36	#33 OR #34 OR #35
#37	#17 AND #32 AND #36

IBS-D, diarrhea-predominant irritable bowel syndrome; FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction; RCT, randomized controlled trial.

https://dx.doi.org/10.21037/apm-22-725

Table S10 The search strategy for the SinoMed database

编号	检索词
#1	“穴位贴敷法”[不加权 : 扩展]
#2	“穴位疗法”[不加权 : 扩展]
#3	“穴位研究”[不加权 : 扩展]
#4	“投药 , 皮肤”[不加权 : 扩展]
#5	“穴位敷贴”[常用字段 : 智能]
#6	“敷贴”[常用字段 : 智能]
#7	“穴位贴敷”[常用字段 : 智能]
#8	“贴敷”[常用字段 : 智能]
#9	“穴位贴”[常用字段 : 智能]
#10	“经穴给药”[常用字段 : 智能]
#11	“中药敷贴”[常用字段 : 智能]
#12	“中药贴敷”[常用字段 : 智能]
#13	“膏贴”[常用字段 : 智能]
#14	“脐贴”[常用字段 : 智能]
#15	“贴脐”[常用字段 : 智能]
#16	“敷脐”[常用字段 : 智能]
#17	“脐疗”[常用字段 : 智能]
#18	“三伏贴”[常用字段 : 智能]
#19	“伏九贴”[常用字段 : 智能]
#20	“三九贴”[常用字段 : 智能]
#21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22	“肠易激综合征”[不加权 : 扩展]
#23	“腹泻”[不加权 : 扩展]
#24	“胃肠疾病”[不加权 : 扩展]
#25	“结肠疾病 , 功能性”[不加权 : 扩展]
#26	“腹泻型肠易激综合征”[常用字段 : 智能]
#27	“腹泻型肠易激综合症”[常用字段 : 智能]
#28	“腹泻型肠易激综合证”[常用字段 : 智能]
#29	“功能性腹泻”[常用字段 : 智能]
#30	“功能性胃肠功能紊乱”[常用字段 : 智能]
#31	“功能性胃肠疾病”[常用字段 : 智能]
#32	“FGID”[常用字段 : 智能]
#33	“结肠易激”[常用字段 : 智能]
#34	“结肠功能紊乱”[常用字段 : 智能]
#35	“肠脑轴”[常用字段 : 智能]
#36	“肠脑互动障碍”[常用字段 : 智能]
#37	“肠 - 脑功能紊乱”[常用字段 : 智能]
#38	“DGBI”[常用字段 : 智能]
#39	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
#40	“随机对照试验”[不加权 : 扩展]
#41	“临床研究”[不加权 : 扩展]
#42	“随机”[常用字段 : 智能]
#43	“对照”[常用字段 : 智能]
#44	“RCT”[常用字段 : 智能]
#45	“临床研究”[常用字段 : 智能]
#46	“疗效观察”[常用字段 : 智能]
#47	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48	#21 AND #39 AND #47

FGID, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction; RCT, randomized controlled trial.

https://dx.doi.org/10.21037/apm-22-725

Table S11 The search strategy for the CiNii database

数	検索用語
#1	過敏性腸症候群 (ALL)
#2	下痢型過敏性腸症候群 (ALL)
#3	下痢 (ALL)
#4	機能性下痢 (ALL)
#5	機能性胃腸障害 (ALL)
#6	機能性胃腸疾患 (ALL)
#7	過敏性結腸 (ALL)
#8	過敏性腸 (ALL)
#9	腸脳 (ALL)
#10	腸脳軸 (ALL)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	東洋医学 (ALL)
#13	伝統的な中国医学 (ALL)
#14	経穴 (ALL)
#15	ツボ (ALL)
#16	ツボ療法 (ALL)
#17	経絡 (ALL)
#18	漢方薬 (ALL)
#19	漢方パッチ (ALL)
#20	ツボの応用 (ALL)
#21	ツボの適用 (ALL)
#22	へそ療法 (ALL)
#23	ハーブパッチ (ALL)
#24	へそパッチ (ALL)
#25	経皮パッチ (ALL)
#26	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#11 AND #26

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