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Systematic Review
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The Effects of Acupuncture on Crohn's Disease: a systematic review and meta-analysis

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Objectives: Crohn's disease is a chronic gastrointestinal disease that belongs to inflammatory bowel disease. This systematic review aims to assess the level of evidence in randomized controlled trials (RCTs) on the effects of acupuncture for Crohn's disease.
Methods: We searched 12 databases from the date of the establishment of each database up to May, 2023 for relevant RCTs. The risk of bias of each study was assessed independently by three reviewers. The level of evidence of meta-analysis was assessed using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).
Results: A total of 12 studies were included. The effective rate (odds ratio [OR] 3.23, 95% confidence interval [CI] 1.43, 7.30) for mild to moderate Crohn's disease patients showed a significant difference between the acupuncture with moxibustion group and the sham-acupuncture with sham-moxibustion group. CDAI change (mean difference [MD] −74.15, 95% CI −93.28, −55.01) for mild to moderate Crohn's disease showed a significant difference between the acupuncture with moxibustion group and the sham-acupuncture with sham-moxibustion group.
Conclusion: Although acupuncture with moxibustion showed significant effects compared to sham-acupuncture with sham-moxibustion, the effect of acupuncture alone is inconclusive. Moreover, only the effect of acupuncture treatment on mild to moderate Crohn's disease patients was derived as a remarkable result. To confirm the effectiveness of acupuncture treatment for Crohn's disease, studies using only acupuncture for intervention or more RCTs targeting various Crohn's disease patients according to the CDAI are required.

Keywords: Crohn's disease, acupuncture, systematic review, meta-analysis

INTRODUCTION

Crohn's disease is a chronic and recurrent gastrointestinal (GI) disease that belongs to the category of inflammatory bowel disease, along with ulcerative colitis. Persistent diarrhea, abdominal pain, rectal bleeding, fever, weight loss, and fatigue can reduce the quality of life in patients with Crohn's disease. Currently, treatment includes anti-inflammatory or immunosuppressive drugs, such as 5-aminosalicylic acid, corticosteroids, antibiotics, and biological agents. However, these have a high risk of side effects.

Crohn's disease may occur anywhere in the GI tract from the mouth to the anus [1]. The exact etiology of the disease is still unknown, but is thought to include immune system imbalances, gut microbiota dysbiosis, and environmental factors [2]. For the diagnosis of Crohn's disease, GI tract endoscopy and cross-sectional imaging of the intestinal wall layers are used, and the severity of the disease is evaluated through indicators ,such as the Crohn's Disease Activity Index (CDAI) or the Inflammatory Bowel Disease Questionnaire (IBDQ) [1].

Although Crohn's disease has the highest prevalence in North America and Europe, its incidence in these regions is fortunately decreasing. Conversely, in regions undergoing industrialization and westernization, such as Africa, Asia, and South America,

the incidence of Crohn's disease has been steadily increasing since 1990 [3]. Currently, the treatment of Crohn's disease in these countries generally follows medical guidelines. However, due to economic burdens or systemic problems, many countries (excluding some developed countries) have restrictions on the use of certain drugs, such as biological agents [4]. Considering this acupuncture may be beneficial to patients with Crohn's disease when used in conjunction with medications. Previous studies have demonstrated the effectiveness of acupuncture in many GI diseases [5], including chemotherapy-induced nausea and vomiting [6], nausea and vomiting after surgery [7, 8], peptic ulcer [9], postoperative ileus [10], irritable bowel syndrome [11], diarrhea [11], colic [12], and ulcerative colitis [13].

To date, available meta-analyses have not included the effect of acupuncture on Crohn's disease. Unlike ulcerative colitis, which may be cured completely by complete colectomy and rectectomy, Crohn's disease is difficult to cure because the inflammation can appear in the entire GI tract, and can recur easily in other parts of the body even if the inflamed part is removed [14]. Therefore, it is important to investigate the therapeutic effect of acupuncture, as an alternative and daily conservative treatment. This study aimed to systematically review existing clinical trials that included acupuncture for the treatment of Crohn's disease and present the evidence relating to its effectiveness.

MATERIALS AND METHODS

1. Criteria for inclusion and exclusion

This study examined only randomized controlled trials (RCTs). RCTs that investigated the effect of acupuncture on Crohn's disease were considered. There was no criterion for blinding. Literature selection and the classification criteria were established according to the PICO-SD as follows. (1) Study Design: Only RCTs written in English, Chinese, and Korean were selected. (2) Patients: There were no exclusion criteria based on patients' age, sex, severity of disease, or treatment period. (3) Interventions: Acupuncture was selected as the treatment intervention but the type of acupuncture was not restricted. (4) Comparisons: No exclusion criteria were set for comparisons. (5) Outcome: The outcome criteria were not determined in advance.

2. Literature searches

Four Korean databases were searched for studies that described acupuncture treatment for Crohn's disease: Research Information Sharing Service (RISS), Korean studies Information Service System (KISS), National Digital Science Library (NDSL), and Korean Medical Database (KMBASE). Seven foreign databases were also included: PubMed, Embase, EBSCO Information Services, Web of Science, the Cochrane Central Register of Controlled Trials, the China National Knowledge Infrastructure (CNKI), and WANFANG. Data up to May 2023 in PubMed and Embase, and up to May 2021 in other databases were retrieved. The searched terms re presented in Supplementary File 1.

3. Data selection

After three reviewers (JH, SY, and SE) independently eliminated duplicate studies obtained from the 12 databases, the titles and abstracts of each remaining study were checked. In total, we reviewed the full text of 12 studies that met the inclusion criteria for eligibility and quality.

4. Data extraction

Three reviewers (JH, SY, and SE) investigated the authors, publication year, intervention, comparative intervention, sample size, treatment period of the intervention and control groups, evaluation tools, outcomes, and adverse effects of the selected studies. When it was difficult to make a clear evaluation, it was decided after discussion with the co-author (HI).

5. Quality evaluation of acupuncture treatment methods based on STRICTA 2010

The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) is an official extension of CONSORT 2010. It provides reporting guidelines on the rationale of acupuncture, details on needling, treatment regimen, different treatment components, practitioner background, and control or comparator interventions [15]. Three reviewers (JH, SY, and SE) independently investigated each study's acupuncture treatment method based on the STRICTA 2010 guidelines,.

6. Quality and risk of bias assessment

The risk of bias was independently assessed by the three reviewers (JH, SY, and SE) using the RoB 2.0 (Version 2.0 of the Cochrane risk-of-bias tool for randomized trials). The RoB 2.0

included the following parameters: 1) randomization process, 2) deviations from intended interventions, 3) missing outcome data, 4) outcome measurement, and 5) reported result selection. Each study was judged as 'High', 'Low', or 'Some concerns'.

7. The level of evidence (GRADE)

The quality of the evidence included in the meta-analysis was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines [16]. GRADE assessed the following items: risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, plausible confounding, and dose response gradient. Results of the assessment were classified as 'high' or 'moderate' or 'low' or 'very low'.

8. Data analysis

Data was presented as odds ratios (OR) or a mean differences (MD) with 95% confidence intervals (CI) for the primary and other outcomes. Data was pooled using Review Manager version 5.4. Statistical heterogeneity was analyzed for each meta-analysis using the Chi-squared test. Study heterogeneity was tested using a standard I^2 statistic. If I^2 was lower than 50%, heterogeneity was considered low. The entire meta-analysis was conducted using a random effect model. A meta-analysis was performed when subgroup analysis was necessary.

The protocol for this study was registered in PROSPERO (CRD42021274139).

RESULTS

1. Study characteristics

In total, 1,273 articles were identified from 12 databases. After eliminating duplicates, 941 articles remained. After screening the titles and abstracts, 39 articles were retained. Finally, after reviewing the full text of the 39 articles, 12 RCTs [17-28] fulfilled the eligibility criteria for inclusion. The flow chart of the study selection and exclusion criteria is shown in Fig. 1.

A detailed description of the characteristics of the included studies is presented in Table 1. A brief overview of the studies is as follows.

We conducted a systematic review on 12 studies, involving 650 participants. In two of the studies [19, 27], a combination of acupuncture and moxibustion was performed in the intervention group, while medication was given to the control group. However, these two studies drew different conclusions from the same RCTs and were considered two different studies in this systematic review. However, since it was the same RCT, it was considered as only one RCTs in the meta-analysis. In seven [20, 22-26, 28] of the remaining nine studies, a combination

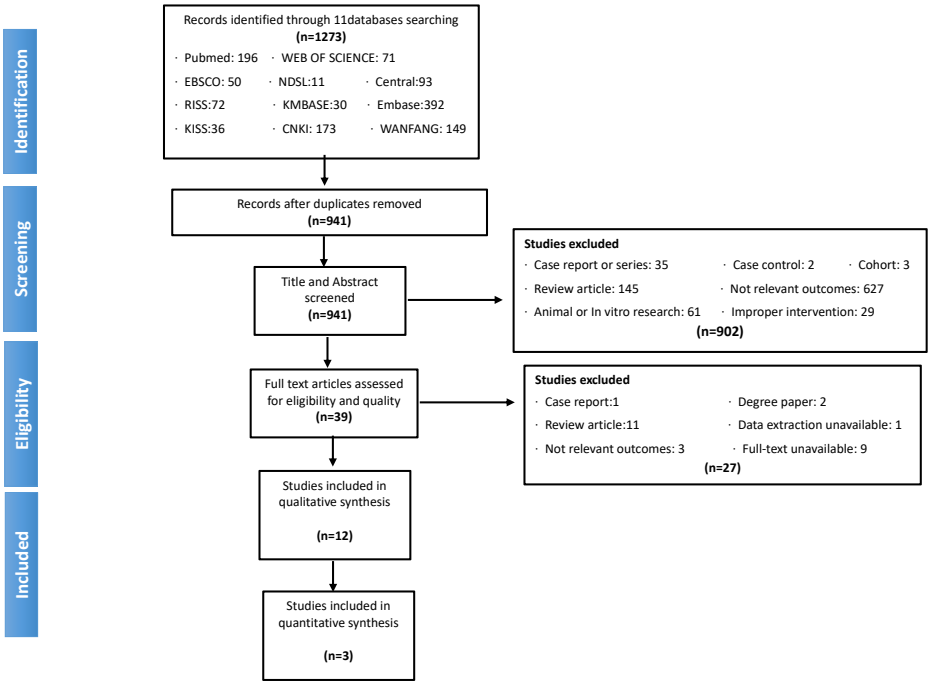

Figure 1. Flow chart of the trial selection process.

Table 1. Summary of randomized controlled trials of acupuncture for Crohn's disease

First author (year)	Each intervention (number)	Treatment period	Acupoint	Outcome	Result		Adverse effect
					Within group (p-value)	Between group (p-value)	
Shang (2015) [19]	(A) HMA (10) (B) MESA (10)	(A) 12 weeks (6 times a week) (B) 12 weeks (4 times a day)	SET 1: MX: ST25, RN6, RN9 AC: ST36, ST37, LI11, LI4 SET 2: MX: BL23, BL25 AC: EX-B2 OF T6-T1 SET 1, 2 were used alternatively each time for HMA GROUP	1) OC exp 2) CL-1 exp 3) ZO-1 exp 4) OC mRNA exp 5) CL-1 mRNA exp 6) ZO-1 mRNA exp	1) A: ↑ ($p = 0.021$), B: ↑ ($p = 0.026$) 2) A: ↑ ($p = 0.016$), B: ns ($p = 0.935$) 3) A: ↑ ($p \leq 0.001$), B: ↑ ($p = 0.016$) 4) A: ↑ ($p = 0.017$), B: ↑ ($p = 0.042$) 5) A: ↑ ($p = 0.017$), B: ↑ ($p = 0.041$) 6) A: ↑ ($p \leq 0.001$), B: ↑ ($p \leq 0.001$)	1) ns ($p = 0.512$) 2) ns ($p = 0.055$) 3) A > B ($p = 0.047$) 4) ns ($p = 0.748$) 5) ns ($p = 0.388$) 6) A > B ($p = 0.023$)	NR
Shi (2011) [27]	(A) HMA (30) (B) MESA (30)	(A) 12 weeks (6 times a week) (B) 12 weeks (4 times a day)	SET 1: MX: ST25, RN6, RN9 AC: ST36, ST37, LI11, LI4 SET 2: MX: BL23, BL25 AC: EX-B2 OF T6-T1 SET 1, 2 were used alternatively each time for HMA GROUP	1) TNF-α reduction (N = A: 10, B: 10) 2) TNFR1 reduction (N = A: 10, B: 10) 3) TNFR2 reduction (N = A: 10, B: 10) 4) AR reduction (N = A: 10, B: 10) 5) Effective rate (N = A: 30, B: 30) 10 people were randomly selected from group (A) and group (B) respectively for outcome 1)-4), while 30 people were fully tested for outcome 5)	1) A, B: ↑ ($p < 0.01$) 2) A, B: ↑ ($p < 0.01$) 3) A, B: ↑ ($p < 0.01$) 4) A, B: ↑ ($p < 0.01$) 5) A: 86.67%, B: 63.33% ($p < 0.05$)	1) A > B ($p < 0.05$) 2) A > B ($p < 0.05$) 3) ns (NR) 4) A > B ($p < 0.05$) 5) A > B ($p < 0.05$)	NR

Table 1. Continued

First author (year)	Each intervention (number)	Treatment period	Acupoint	Outcome	Result		Adverse effect
					Within group (p-value)	Between group (p-value)	
Bao (2021) [20]	(A) ACM (32) (B) SACSM (31)	(A), (B): 12 weeks (3 times a week)	AC: CV12, ST37, SP6, SP4, LI4, LI11, KI3, LR3 MX: ST25, ST36	1) HADS-A reduction 2) HADS-D reduction 3) Abdominal pain 4) Diarrhea frequency 5) IDO1 concentration 6) Kyn/Trp 7) KynA/KyN 8) QuinA/Kyn reduction 9) KynA/QuinA	1) A: ↑ ($p < 0.01$), B: ↑ ($p > 0.05$) 2) A: ↑ ($p < 0.05$), B: ns ($p > 0.05$) 3) A, B: ↓ ($p < 0.001$) 4) A: ↓ ($p < 0.05$), B: ns (NR) 5) A: ↓ ($p < 0.001$), B: ↓ ($p < 0.05$) 6) A: ↓ ($p < 0.05$), B: ns (NR) 7) A: ↑ ($p < 0.05$), B: ns (NR) 8) A: ↑ ($p < 0.01$), B: ns (NR) 9) A: ↑ ($p < 0.01$), B: ns (NR)	1) A > B ($p < 0.01$) 2) NS ($p > 0.05$) 3) A > B ($p < 0.05$) 4) A > B ($p < 0.05$) 5) A > B ($p < 0.01$) 6) ns 7) ns 8) A > B ($p < 0.01$) 9) A > B ($p < 0.05$)	NR
Bao (2017) [18]	(A) EA (18) (B) MX (20)	(A), (B): 12 weeks (3 times a week)	Both: ST25 (bilateral), CV6, CV12	1) CDAI 2) IBDQ 3) RsFC increase	1) A, B: ↓ ($p < 0.01$) 2) A, B: ↑ ($p < 0.01$) 3) A, B: ↑ ($p < 0.05$)	1) ns ($p = 0.634$) 2) ns ($p = 0.93$) 3) 1. A > B (between Bi.Hip and L.MCC and R.Insula) ($p < 0.05$) 2. A < B (between L. Hip and R.Precuneus and L.IPC) ($p < 0.05$)	NR
Bao (2018) [26]	(A) WMA (26) (B) SMA (21)	(A), (B): 12 weeks (3 times a week)	MX: ST25, ST36 (bilateral) AC: ST37, SP6, SP4, LR3, KI3, LI4, LI11	1) CDAI 2) IBDQ 3) SAS 4) SDS 5) Complete remission 6) Clinical response	1) A, B: ↓ ($p = 0.016$) 2) A: ↑ ($p \leq 0.001$), B: ns ($p = 0.006$) 3) A: ↓ ($p = 0.006$), B: ns ($p = 0.010$) 4) A: ↓ ($p = 0.013$), B: ns ($p = 0.033$) 5) A: 84.62% ($p = 0.016$), B: 52.38% ($p = 0.016$) 6) A: 80.77% ($p \leq 0.001$), B: 19.05% ($p \leq 0.001$)	1) A > B ($p \leq 0.001$) 2) A > B (NR) 3) A > B (NR) 4) A > B (NR) 5) A > B (NR) 6) A > B (NR)	Ecchymoma in WMA (1)

Table 1. Continued

First author (year)	Each intervention (number)	Treatment period	Acupoint	Outcome	Result		Adverse effect
					Within group (p-value)	Between group (p-value)	
Zhao (2015) [22]	(A) HMAC (10) (B) WMSA (10)	12 weeks (3 times a week)	(A) HM: ST25, CV6, CV12 AC: ST36, ST37, SP6, KI3, SP4, LR3 (B) WM: ST25, CV6, CV12 SA: 1-2 cm away from ST36, ST37, SP6, KI3, SP4, LR3	1) CDAI 2) Ratio of Th17, Treg cells 3) IL-17 Protein 4) IL-17 mRNA 5) RORγt protein 6) RORγt mRNA 7) FOXP3 protein 8) FOXP3 mRNA	1) A, B: ↓ (ns) 2) A: ↓ ($p < 0.01$), B: ↓ ($p < 0.05$) 3) A, B: ↓ ($p < 0.01$) 4) A, B: ↓ ($p < 0.05$) 5) A: ↓ ($p < 0.01$), B: ns 6) A: ↓ ($p < 0.05$), B: ns 7) A: ↑ ($p < 0.05$), B: ns 8) A: ↑ ($p < 0.01$), B: ns	1) A > B ($p = 0.002$) 2) ns 3) A < B ($p < 0.01$) 4) A < B ($p < 0.01$) 5) A < B ($p < 0.01$) 6) A < B ($p < 0.01$) 7) A < B ($p < 0.01$) 8) A < B ($p < 0.01$)	NR
Bao (2016) [17]	(A) EA (30) (B) HM (30)	12 weeks (3 times a week)	Both: ST25, CV6, CV12	1) SAS 2) SDS 3) Abdominal pain scores 4) Bowel sounds/flatus scores 5) General fatigue	1) A, B: ↓ ($p < 0.01$) 2) A, B: ↓ ($p < 0.01$) 3) A: ↓ ($p < 0.01$, 0.05), B: ↓ ($p < 0.01$) 4) A, B: ↓ ($p < 0.01$) 5) A: ↓ ($p < 0.01$), B: ↓ ($p < 0.05$)	1) ns 2) ns 3) ns 4) ns 5) ns	NR
Bao (2016) [23]	(A) HMAC (51) (B) WMSA (51)	12 weeks (3 times a week)	(A) HM: ST25, CV6, CV12 AC: ST36, ST37, SP6, KI3, SP4, LR3 (B) HM: ST25, CV6, CV12 AC: 1-2 cm away from ST36, ST37, SP6, KI3, SP4, LR3	1) Abdominal pain relief 2) Diarrhea symptom relief 3) Other symptoms relief (tired, poor appetite, bowel, cold limbs, sore waist and knees, tensile and heavy)	1) A: ↓ ($p < 0.01$), B: ↓ ($p < 0.01$, 0.05) 2) A: ↓ ($p < 0.01$), B: ↓ ($p < 0.01$, 0.05) 3) A, B: ↓ ($p < 0.01$)	1) A > B ($p < 0.01$) 2) A > B ($p < 0.01$) 3) A > B ($p < 0.01$)	Subcutaneous Hematoma (1) mild scald (1)
Bao (2016) [21]	(A) EA (16) (B) HM (18)	12 weeks (3 times a week)	Both: ST25, CV6, CV12	1) CDAI 2) IBDQ	1) A, B: ↓ ($p < 0.001$) 2) A, B: ↑ ($p < 0.01$)	1) ns 2) ns	NR

Table 1. Continued

First author (year)	Each intervention (number)	Treatment period	Acupoint	Outcome	Result		Adverse effect
					Within group (p-value)	Between group (p-value)	
Bao (2014) [24]	(A) HMA (46) (B) WMSA (46)	12 weeks (3 times a week)	(A) AC: ST36, ST37, SP4, SP6, KI3, LR3 MX: ST25, CV6, CV12 (B) AC: 20 mm away from ST36, ST37 Between LR4, SP4 15 mm away from SP6, K13 Between LR3, SP3 MX: ST25, CV6, CV12	1) CDAI 2) IBDQ 3) CRP 4) ESR 5) HGB 6) CDEIS 7) HS 8) Effective rate	1) A, B: ↓ ($p \leq 0.001$) 2) A, B: ↑ ($p \leq 0.001$) 3) A :↑ ($p = 0.007$), B: ns (NR) 4) A, B: ↓ (NR) 5) A: ↑ ($p = 0.026$), B: ns (NR) 6) A, B: ↓ (NR) 7) A: ↓ ($p = 0.002$), B: ↓ (NR) 8) A: 78.26% ($p \leq 0.001$), B: 36.96% ($p \leq 0.001$)	1) A > B ($p \leq 0.001$) 2) A > B ($p = 0.017$) 3) A > B ($p = 0.008$) 4) ns ($p = 0.163$) 5) A > B ($p = 0.029$) 6) ns ($p = 0.380$) 7) A > B ($p = 0.029$) 8) A > B ($p \leq 0.001$)	Subcutaneous Hematoma(1) mild burn(2)
Joos (2004) [25]	(A) TMA (27) (B) MA (24)	4 weeks (1-2 w: 3 times a week 3-4 w: 2 times a week)	(A) AC: BL20, CV12, ST36, ST25 in alternation SP15 (B) Non-acupoints	1) CDAI 2) IBDQ 3) VAS 4) α_1-GP, mg/dL 5) CRP, mg/dL 6) Effective rate	1) A: ↓ ($p = 0.073$), B: ↓ (NR) 2) A, B: ↑ (NR) 3) A: ↓ ($p = 0.045$), B: ↓ (NR) 4) A: ↓ ($p = 0.046$), B: ↓ (NR) 5) A, B: ns (NR) 6) A: 41% ($p = 0.095$), B: 33% ($p \leq 0.001$)	1) A > B ($p < 0.003$) 2) ns (NR) 3) A > B ($p < 0.045$) 4) ns (NR) 5) ns (NR) 6) A > B ($p = 0.095$)	NR
Bao (2022) [28]	(A) ACM (32) (B) SACSM (31)	12 weeks (3 times a week)	Both: CV12, ST37, SP6, SP4, LR3, KI3, LI4, LI11 (A) MX: ST36, ST25 (B) MX: 8-10 cm away from ST36, ST25	1) Remission rate 2) CDAI 3) Clinical response rate 4) CRP 5) CDEIS 6) HS	1) A: ↑ (NR), B: ↓ (NR) 2) A, B: ↓ ($p < 0.001$) 3) A, B: ↑ (NR) 4) A: ↓ ($p < 0.001$), B: ns ($p < 0.001$) 5) A: ↓ ($p = 0.001$), B: ↓ ($p = 0.131$) 6) A: ↓ ($p < 0.001$), B: ↓ ($p = 0.104$)	1) A > B ($p = 0.001$) 2) A > B ($p < 0.001$) 3) A > B ($p < 0.001$) 4) A > B ($p = 0.037$) 5) A > B ($p = 0.015$) 6) A > B ($p = 0.002$)	NR

HMA, herb-partitioned moxibustion and acupuncture; MESA, mesalazine; MX, moxibustion; AC, acupuncture; OC, occludin; cl-1, claudin-1; ZO-1, zonula occludens-1; exp, expression; ns, not statistically significant different; NR, not reported; AR, apotosis rate; ACM, acupuncture combined with moxibustion; SACSM, sham acupuncture combined with sham moxibustion; HADS, Hospital Anxiety and Depression Scale; IDO1, gastrointestinal indoleamine 2,3-dioxygenase; Trp, tryptophane; QuinA, quinolic acid; KynA, kynurenic acid; RsFc, Resting State Functional Connectivity; Hip, hippocampus; Bi, Bilatral; MCC, middle cingulate cortex; IPC, inferior parietal lobe; WMA, warm moxibustion combined with acupuncture; SMA, sham warm moxibustion combined with acupuncture; CDAI, Crohn's disease activity index; IBDQ, inflammatory bowel disease questionnaire; SAS, self-rating anxiety scale; SDS, self-rating depression scale; WMSA, wheat bran-partitioned moxibustion and acupuncture; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; CDEIS, Crohn's disease endoscopic index of severity; HS, histopathological scores; TMA, TCM with moxibustion and acupuncture; MA, minimal acupuncture; VAS, visual analogue scale; α_1-GP, α_1-acid glycoprotein; WM, wheat bran-partitioned moxibustion; TCM, traditional Chinese medicine; HS, histopathological score.

therapy of acupuncture and moxibustion was performed in the intervention group, while sham-acupuncture and sham-moxibustion treatment were performed in the control group. In the remaining three [17, 18, 21] studies, electro-acupuncture (EA) was performed in the intervention group, while moxibustion was performed in the control group. These three studies investigated the effects of acupuncture and moxibustion in patients with Crohn's disease, respectively.

In most studies, CDAI was set as an outcome measurement. As aforementioned, CDAI is a measuring tool that indicates the activity of Crohn's disease. CDAI < 150 represents that the disease is in remission, while CDAI ≥ 150 the disease is in its active stage. The remission stage refers to the patient being asymptomatic, while the active stage describes a patient with symptoms. Moreover, the active stage is divided into three sub-stages using the CDAI index: 150 ≤ CDAI < 220 = mild, 220 ≤ CDAI < 450 = moderate, and CDAI ≥ 450 = o severe (Table 1) [1].

2. Adverse events

Adverse events were reported in three RCTs [23, 24, 26]. Side effects, such as subcutaneous hematoma during acupuncture occurred in two patients in the treatment group, and a mild burning sensation occurred during moxibustion in one patient in the control group. Moreover, ecchymoma occurred in one patient in the treatment group. No serious adverse events were reported in all RCTs (Table 1).

3. Risk of bias (Fig. 2) [29]

1) Randomization process

According to the randomization process, five RCTs [17, 18, 20, 24, 28] were classified as "low risk", while seven RCTs [19, 21-23, 25-27] were noted as "some concerns".

2) Deviation from the intended interventions

According to the deviations from the intended interventions, two RCTs [22, 26] were classified as "some concerns", while ten RCTs [17-21, 23-25, 27, 28] were noted as "low risk".

3) Missing outcome data

According to the missing outcome data, three RCTs [20, 21, 23] were classified as "high risk", and nine RCTs [17-19, 22, 24-28] were classified as "low risk".

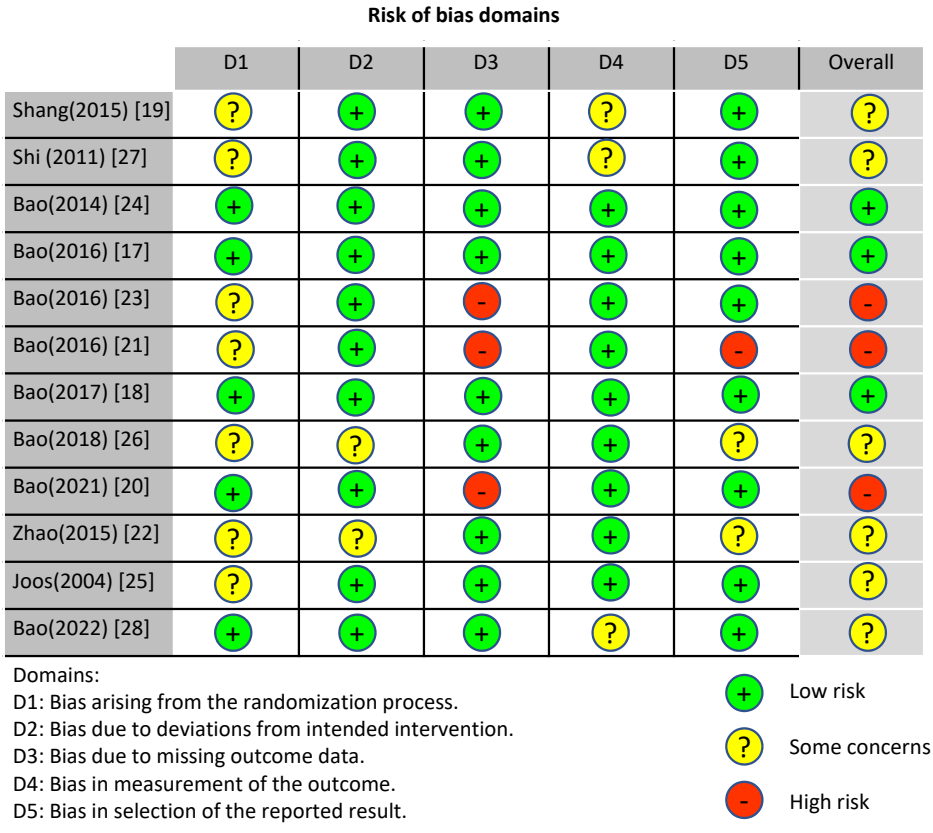

Figure 2. Risk of bias assessed using the Cochrane "Risk of bias 2.0" tool. +, low risk of bias; -, high risk of bias; ?, some concern of bias.

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4) Outcome measurements

According to the outcome measurements, three RCTs [19, 27, 28] were classified as "some concerns", and nine RCTs [17, 18, 20-26] were judged as "low risk".

5) Reported result selection

According to the selection of reported results, one RCTs [21] was classified as "high risk", two RCTs [22, 26] as "some concerns", and nine RCTs [17-20, 23, 25, 27, 28] as "low risk".

6) Overall bias

Three RCTs [17, 18, 24] were evaluated as "low risk", three RCTs [20, 21, 23] as "high risk", and six RCTs [19, 22, 25-28] as "some concerns".

4. STRICTA 2010

STRICTA is a guideline designed to improve the reporting standards for interventions in acupuncture clinical trials. It is also used as an additional guideline for acupuncture RCTs. STRICTA aims to reduce the risk of errors or biases in the design of acupuncture intervention studies through 20 types of check lists and enabling better understanding and interpretation of results [15]. As a result of the response, Item 3, which corresponds to the treatment regimen, and Item 4, which corresponds to other components of treatment, showed a high response rate with an average of 90%-100% for all items. In Item 2, which corresponds to the details for needling, only the number of needle insertions per subject per session (2a, 0%) and needle stimulation (2e, 50%) showed a low response rate. Otherwise, all questions relating to Item 2 showed a high response rate (80%-100%). Item 2a asks the number of needles used per patient, but none of the studies provided this information. Item 2d asks whether a response was triggered by acupuncture; ten [17, 18, 20, 22-28] out of 12 studies stated that 'de-qi(得氣)' resulted. Items with low response rates included the "style of acupuncture" (1a, 42%), "reason for treatment" (1b, 25%), and "practitioner background" (5, 33%), and "rationale for the control or comparator" (6a, 58%), respectively.

Bao et al.'s 2014 study [24] that recorded the highest response rate of 88%, and the lowest omission rate of 12%. On the other hand, three studies [21-23] recorded the lowest response rate (65%), and the highest omission rate (35%). Table 2 presents a detailed description of each study's STRICTA checklist results.

5. Meta-analysis

Two studies [19, 27] that originated from the same RCT presented different results in each of the study. These two studies were the only ones that treated the control group with medication. Therefore, a meta-analysis comparing the effects of acupuncture and medication was not performed due to the absence of samples. Seven [20, 22-26, 28] of the remaining ten studies combined the use of acupuncture and moxibustion in the treatment group. The remaining three studies [17, 18, 21] were all single studies (electro-acupuncture was used in the treatment group, and moxibustion was treated in the control group). Meta-analyses for the single studies were performed to compare the effects of acupuncture and moxibustion treatment. In the meta-analyses, all mild to moderate cases of Crohn's disease were in the CDAI range of 150-350, while all mild Crohn's disease were < 150.

1) Effectivity rate

A total of three studies [24-26] had effective rate rates. These studies used acupuncture with moxibustion as the intervention, while the intervention for the control group was sham-acupuncture with sham-moxibustion. Moreover, the effective rate was calculated from the proportion of patients with a CDAI of less than 150 among those with a CDAI of 150 to 350 (mild to moderate active stages). The endpoint effective rate was derived from these three studies using a meta-analysis (Fig. 3) The odds ratio (OR) for acupuncture compared to that of sham-acupuncture was 3.23 (95% confidence interval [CI] 1.43, 7.30; p = 0.005; n = 190; I^2 = 38%), indicating that acupuncture is more effective.

2) CDAI results after treatment

A total of two studies [25, 26] used acupuncture with moxibustion as the intervention, while the control group used sham-acupuncture with sham-moxibustion. The CDAI results in these two studies ranged from mild to moderate (including patients with CDAI 150-350). A meta-analysis of these studies was performed to determine the endpoint CDAI results for the mild to moderate Crohn's disease cases (Fig. 4). The result showed a mean difference (MD) of −25.01 (95% CI −44.70, −5.32; p = 0.01; n = 98; I^2 = 0%), indicating that acupuncture provided statistically significant differences (when comparing between the acupuncture and sham-acupuncture groups).

Table 2. STRICTA 2010

First author (year)	1. Acupuncture rationale			2. Details of needling							3. Treatment regimen		4. Other components of treatment		5. Practitione background	6. Control intervention	
	1a	1b	1c	2a	2b	2c	2d	2e	2f	2g	3a	3b	4a	4b	5	6a	6b
Shang (2015) [19]	CAM	Chiense national acupoint standard	ST	NR	ST36, ST37, LI11, LI4, EX-B2 of T6-T1	20 to 40 mm into acupoints	NR	NR	NR	Huatuo, Suzhou, China (0.30 × 40 mm)	72	12 weeks (6 times a week)	HM	Informed consent	Qualified and skilled physician	R	Mesa
Shi (2011) [27]	NR	NR	ST	NR	ST36, ST37, LI11, LI4, EX-B2 OF T6-T1	Puncture directly 20 to 40 mm into acupoints	De-QI sensation	MA	30 min	Huatuo, Suzhou, China (0.30 × 40 mm)	72	12 weeks (6 times a week)	HM	Informed consent	NR	R	Mesa
Bao (2021) [20]	NR	NR	ST	NR	CV12, ST37, SP6, SP4, LI4, LI11, KI3, LR3	Puncture directly 20 to 25 mm into acupoints	De-QI sensation	MA	30 min	Disposable external cannula type acupuncture 0.30 × 40 mm or sterile acupuncture 0.30 × 25 mm	36	12 weeks (3 times a week)	Mx	Informed consent	Experienced practicing Chinese physicians	R	Sham-AC and MX
Bao (2017) [18]	CAM	AC literature	ST	NR	ST25 (bi), CV6, CV12	Rapidly inserted to skin and slowly inserted 20 to 25 mm into subcutaneous region	De-QI sensation	EA	30 min	Huatuo, Suzhou medical appliance factory (0.30 ×40 mm)	36	12 weeks (3 times a week)	None	NR	NR	R	HM
Bao (2018) [26]	NR	NR	ST	NR	ST37, SP6, SP4, LR3, KI3, LI4, LI11	NR	De-QI sensation	NR	30 min	NR	36	12 weeks (3 times a week)	Mx	Informed consent	NR	R	Sham-AC and MX
Zhao (2015) [22]	NR	NR	ST	NR	ST36, ST37, SP6, KI3, SP4, LR3	20 to 30 mm into the skin	De-QI sensation	NR	30 min	Huatuo, Suzhou, China (0.30 ×40 mm or 25 mm)	36	12 weeks (3 times a week)	HM	Informed consent	NR	NR	SA
Bao (2016) [17]	NR	NR	ST	NR	ST25, CV6, CV12	20 to 25 mm into acupoints	De-QI sensation	EA	30 min	Suzhou, China, HANS-100 (0.30 × 40 mm)	36	12 weeks (3 times a week)	None	Informed consent	NR	NR	HM
Bao (2016) [23]	NR	NR	ST	NR	ST36, ST37, SP6, KI3, SP4, LR3	Puncture 20 to 30 mm into acupoints	De-QI sensation	NR	30 min	Sterile disposable stainless steel needle (0.30 ×40 or 25 mm)	36	12 weeks (3 times a week)	HM	Informed consent	NR	NR	SA

Table 2. Continued

First author (year)	1. Acupuncture rationale			2. Details of needling							3. Treatment regimen		4. Other components of treatment		5. Practitione background	6. Control intervention	
	1a	1b	1c	2a	2b	2c	2d	2e	2f	2g	3a	3b	4a	4b	5	6a	6b
Bao (2016) [21]	NR	NR	ST	NR	ST25, CV6, CV12	Inserted 20 to 25 mm beneath the skin	NR	EA	30 min	Huatuo, Suzhou, China (0.30 × 40 mm) Connected to HANS EA LH100A, Nanjing, China	36	12 weeks (3 times a week)	None	Informed consent	NR	NR	HM
Bao (2014) [24]	TCM	Chinese national acupoint standard	ST	NR	ST36, ST37, SP4, SP6, KI3, LR3	Directly inserted 20 to 30 mm into skin	De-QI sensation	NR	30 min	Sterile disposable stainless steel needles (0.30 × 40 or 25 mm)	36	12 weeks (3 times a week)	HM	Informed consent	Qualified TCM practitioners	R	SA
Joos (2004) [25]	TCM	NR	ST	NR	BL20, CV12, ST36, ST25, SP15	5 to 30 mm into acupoints	De-QI sensation	MA	10 min	Seirin soft needles (0.30 × 30 mm)	10	4 weeks (1-2 w: 3 times a week 3-4 w: 2 times a week)	Mx	Informed consent	Certified trained physi-cian	NR	MiA
Bao (2022) [28]	TCM	NR	ST	NR	CV12, ST37, SP6, SP4, LR3, KI3, LI4, LI11	Vertically inserted into each acupoint to 20-30 mm depth	De-QI sensation	NR	30 min	Hwato, Suzhou, China (0.30 × 40 mm or 0.30 × 25 mm)	36	12 weeks (3 times a week)	Mx	Informed consent	NR	R	Sham-AC and MX

CAM, complementary and alternative medicine; ST, standardized; NR, not reported; MA, manual acupuncture; EA, electro-acupuncture; HM, herb-partitioned moxibustion; Mx, moxibustion; R, reported; Mesa, mesalazine; SA, superficial acupuncture; AT, alternation; MiA, minimal acupuncture.

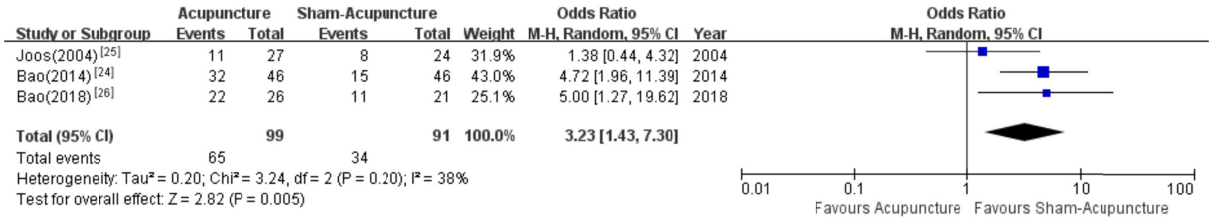

Figure 3. Meta analysis of acupuncture with moxibustion versus sham-acupuncture with sham-moxibustion (effective rate for mild to moderate Crohn's disease patients).

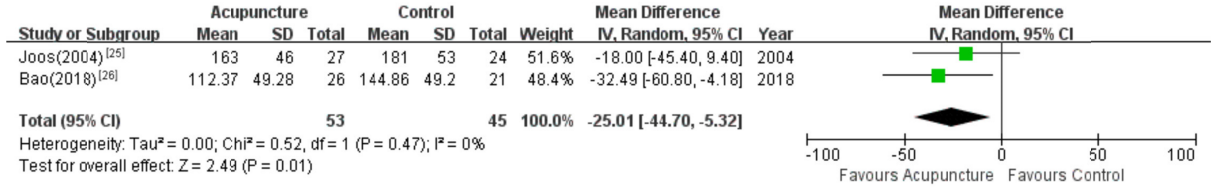

Figure 4. Meta analysis of acupuncture with moxibustion versus sham-acupuncture with sham-moxibustion (CDAI results for mild to moderate Crohn's disease patients).

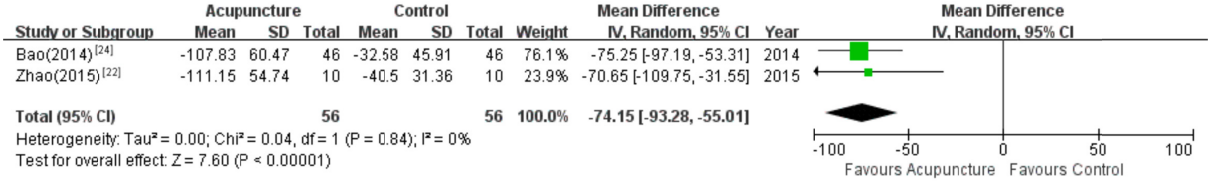

Figure 5. Meta analysis of acupuncture with moxibustion versus sham-acupuncture with sham-moxibustion (CDAI change for mild to moderate Crohn's disease patients).

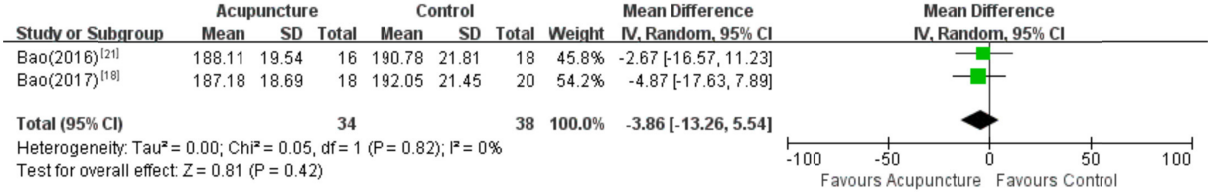

Figure 6. Meta analysis of EA VS Moxibustion (IBDQ results).

3) CDAI changes after treatment

Two studies [22, 24] used acupuncture with moxibustion as the intervention, while sham-acupuncture with sham-moxibustion was used in the control group. These studies included patients with a CDAI of 150-350 (mild to moderate). We used these studies in a meta-analysis to determine the endpoint CDAI changes (Fig. 5). The result showed a MD of –74.15 (95% CI –93.28, –55.01; p < 0.001; n = 112; I^2 = 0%), indicating that acupuncture provided statistically significant differences (when comparing between the acupuncture and sham-acupuncture groups).

4) IBDQ results

Two studies [18, 21] t used EA in the intervention group, and moxibustion in the control group. The presented IBDQ results included patients with mild Crohn's disease (CDAI < 150). A meta-analysis of these two studies was performed to determine the endpoint IBDQ result of the mild Crohn's disease cases (Fig. 6). The results showed an MD of –3.86 (95% CI –13.26, 5.54; p = 0.42; n = 72; I^2 = 0%), indicating that the CDAI of patients with mild Crohn's disease did not show any significant difference after treatment with EA or moxibustion.

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6. The level of evidence (GRADE)

Table 3 shows the level of evidence for each meta-analysis. The studies included in the analyses had a small number of participants, which increased the imprecision in all the analyses. The analysis of the effective rate and CDAI changes for patients with mild to moderate Crohn's disease showed a moderate level of evidence due to the larger effect size in the intervention group. However, the level of evidence in the remaining nine meta-analyses were evaluated as low or very low due to the small sample sizes.

DISCUSSION

The exact pathophysiology of Crohn's disease is unknown. Currently, pharmacological inflammation control is the main form of treatment. However, chronic use of medications can cause unwanted side effects. Conservative treatment, such as acupuncture, may reduce the risk of drug-related adverse effects and greatly improve the patient's quality of life. Three [17, 20, 26] out of the 12 studies in this systematic review included the use of the Hospital Anxiety and Depression Scale (HADS), Self-rating Anxiety Scale (SAS), or Self-rating Depression Scale (SDS), which are all indicators for depression and anxiety. Considering that patients with IBD may be twice as anxious and about 1.6 times more depressed than healthy individuals [30], acupuncture as a conservative treatment should be explored. Moreover, some studies [19, 22, 27] have reported that acupuncture increases the expression of proteins associated with the tight junctions found in cells of the gastrointestinal tract, such as Zonula ocludens-1, occludin, and claudin-1. Acupuncture may reduce the expression of inflammatory cell, proteins, and receptors, such as Th17, Treg, RORγt, IL-17, TNF-α, TNFR1, and TNFR2, while increasing Foxp3 and Treg expression. Considering these, acupuncture may be effective for treating Crohn's disease. Hence, we conducted a systematic review of 12 studies [17-28], with 650 participants, to determine if acupuncture is an effective treatment option for Crohn's disease.

All 12 studies were RCTs. The main indicators were depression and anxiety and indicators relating to inflammation and quality of life, such as the CDAI and IBDQ. Most of the studies used acupuncture and moxibustion together in the treatment group. Among the 14 acupuncture points used in the 12 studies, the most commonly used acupuncture point was ST37 (used in eight studies). Moreover, ST36, SP4, SP6, KI3, LR3, and CV12 were also used frequently. For the meta-analyses, the combination and single studies were divided. A combination study referred to a study in which acupuncture and moxibustion were used together in the intervention group, while a single study referred to a study in which only electro-acupuncture was used for intervention. A meta-analysis was performed for two groups according to disease severity (mild: CDAI < 150

Table 3. The level of evidence and meta-analysis of outcomes

Variable	Overall effect				Studies (N)	Sample size (N)	Level of evidence
	MD or OR	95% CI	p	I^2			
Acupuncture versus control							
CDAI result (mild)	9.13	−4.65, 22.91	0.19	0%	2	72	Low
CDAI result (mild to moderate)	−25.01	−44.7, −5.32	0.01	0%	2	98	Low
CDAI change (mild)	3.71	−9.09, 16.5	0.57	0%	2	72	Low
CDAI change (mild to moderate)	−74.15	−93.28, −55.01	< 0.001	0%	2	112	Moderate
CDAI subgroup (female)	−60.21	−123.23, 2.82	0.06	87%	2	66	Very low
CDAI subgroup (male)	−77.68	−102.37, −52.99	< 0.001	7%	2	65	Low
Treatment with corticosteroids (yes)	−80.51	−128.65, −32.37	0.001	73%	2	40	Very low
Treatment with corticosteroids (no)	−57.89	−86.33, −29.45	< 0.001	42%	2	91	Low
IBDQ result	−3.86	−13.26, 5.54	0.42	0%	2	72	Low
IBDQ change	0.28	−8.15, 8.7	0.95	0%	2	72	Low
CRP change	−2.3	−16.83, 12.23	0.76	90%	2	131	Very low
Effective rate	3.23	1.43, 7.30	0.005	38%	3	190	Moderate

CI, confidence interval; MD, mean difference; OR, odds ratio.

and mild to moderate: CDAI 150-350). A meta-analysis with three RCTs [24-26] revealed that acupuncture and moxibustion were significantly effective in improving the patients' Crohn's disease status (from a mild to moderately active stage to clinical remission) than sham-acupuncture and sham-moxibustion. Another meta-analysis of two other RCTs [25, 26] showed that acupuncture significantly reduced the CDAI in patients with mild to moderate active Crohn's disease. Combining the results of these, acupuncture provided a significant difference in the mild to moderate cases.

In all four meta-analyses performed on patients with mild Crohn's disease (CDAI < 150), electro-acupuncture was performed in the intervention group and moxibustion was performed in the control group. These meta-analyses compared the effects of electroacupuncture and moxibustion on Crohn's disease. Two studies [18, 21] included in these meta-analyses showed a mean CDAI reduction in both the electro-acupuncture treatment group (–28.11 and –26.74, respectively) and the moxibustion treatment group (–30.95 and –31.22, respectively). Considering the IBDQ, the mean increase in the electro-acupuncture group was reported to be 15.44 and 17.28 (in two studies) and 15.95 and 16.00 in the moxibustion group. In summary, although electro-acupuncture and moxibustion were effective in reducing the CDAI score and increasing IBDQ score, respectively, there was no significant difference between the two forms of treatment. Although acupuncture and moxibustion stimulate different regions of the brain, there is likely no significant difference in their inflammatory suppression effects [21].

Previous studies have shown that acupuncture inhibits the inflammation involved in Crohn's disease through the vagus nerve [31] or the neuroreceptor modulation process [32]. Additionally, acupuncture treatment is effective for treating various gastrointestinal diseases and is more effective than medication for the management of ulcerative colitis [13] (also an inflammatory bowel disease category). Considering these, it is reasonable to infer that acupuncture may likely have a positive effect on Crohn's disease. In this study, a high level of evidence was demonstrated through the systematic review and meta-analyses in support of the effect of acupuncture on Crohn's disease. Moreover, our findings confirmed that the CDAI score significantly decreased in patients after acupuncture compared to those who did not have acupuncture.

This study has some limitations. All meta-analyses conducted in this study were performed using a small number of RCTs (2-3) and had a small sample size, which limited the level of evidence. As a result, most meta-analyses performed in this study were evaluated as having low or very low quality of evidence. Moreover, all available RCTs were from a single country (China), which may lead to bias. The meta-analyses that showed significant results also have limitations. In one study [18], acupuncture and moxibustion only elicited responses in different regions of the brain and did not make lead to a significant improvement in the CDAI. The meta-analysis only showed a significant effect after the studies were combined. It is difficult to conclude that the significant effect was derived from acupuncture alone. Importantly, results relating to acupuncture treatment was only for patients with mild to moderate Crohn's disease (CDAI 150-350). The effect of acupuncture on patients with mild Crohn's disease of CDAI ≤ 150, moderate Crohn's disease with CDAI 350-450, and severe Crohn's disease with CDAI ≥ 450, were not disclosed.

Furthermore, a meta-analysis to compare the effects of medication (standard treatment for Crohn's disease) and acupuncture treatment was not possible. Hence, our study can only suggest that acupuncture may be considered as an adjunctive treatment in Crohn's disease. Our results did not provide enough evidence to support acupuncture as a key treatment. In the future, comparative RCTs with a medication group and an acupuncture group, or RCTs that identify the effects of acupuncture treatment on patients with different severity of Crohn's disease according to the CDAI are warranted.

This study is the first systematic review and meta-analysis to support the use of acupuncture in treating Crohn's disease. Moreover, our findings suggest that acupuncture is effective for patients with mild to moderate (CDAI 150-350) Crohn's disease. More studies to expand to the body of knowledge in this field is urgently required.

DATA AVAILABILITY

The data that support the findings of this study are available within the article.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary data is available at https://doi.org/10.3831/KPI.2023.26.3.211.

Supplementary File 1. Search strategy.

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