SYSTEMATIC REVIEW AND META-ANALYSIS

DOI: http://dx.doi.org/10.15403/jgld-5729

The Efficacy of Traditional Chinese Medicine for Crohn's Disease Treatment: A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: Crohn's disease (CD) is an inflammatory bowel disease with limited treatment options for patients with mild to moderately active disease. There is a lack of consensus for using traditional Chinese medicine (TCM) for symptom relief. This review aimed to assess the efficacy of TCM compared to placebo for CD symptom severity relief in patients with mild to moderate CD.

Methods: We searched MEDLINE via PubMed, the Cochrane Library, Scopus, and CINAHL for articles and reviewed results from Web of Science, Google Scholar, clinicaltrials.gov, and reference lists of included studies. We included randomized control trials comparing TCM to placebo in patients with mild to moderate CD to evaluate change in objective symptom severity [Crohn's Disease Activity Index (CDAI) and Crohn's Disease Endoscopic Index of Severity (CDEIS)]. We imported selected articles for dual blinded review, used random-effects models to calculate the mean CDAI and CDEIS differences between TCM and placebo, and qualitatively analyzed differences in inflammatory biomarkers and quality of life.

Results: The search identified 232 relevant studies. We included five studies, totalling 292 participants utilizing acupuncture and herb-partitioned moxibustion. The studies demonstrated a more significant decrease in mean CDAI score due to TCM compared to placebo [-49.91 (95% CI: -64.97, -34.84; p<0.00001); (I^2 = 61%, p=0.03)]. Two studies also demonstrated an overall difference in mean CDEIS between TCM and placebo [-2.96 (95% CI: -6.31, 0.40; p=0.08); (I2 = 53%, p=0.140)]. Improvements in quality of life scores were greater in TCM versus placebo groups. There were mixed results for changes in inflammatory biomarkers.

Conclusion: Our findings suggest that TCM may improve objective CD symptoms compared to placebo. Additional studies with more extensive and diverse populations are necessary to determine TCM's true effects on CD patients.

Key words: traditional Chinese medicine – Crohn disease – Chinese herbal drugs – acupuncture therapy – moxibustion.

Abbreviations: CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; FCC: Fufangkushen colon-coated capsule; RCT: randomized controlled trial; QoL: quality of life; TCM: traditional Chinese medicine; TwHF: Tripterygium wilfordii Hook F; 5-ASA: 5-aminosalicylic acid.

Received: 16.08.2024
Accepted: 30.11.2024

INTRODUCTION

Globally, over 4.9 million adults were diagnosed with inflammatory bowel disease (IBD) in 2019, reflecting a nearly twofold increase in prevalence since 1999 [1-3]. Inflammatory bowel disease, a diagnostic class encompassing both Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation of the gastrointestinal tract, and morbidity associated with the condition significantly and negatively impacts patients' quality of life [2, 4, 5]. The focus of this systematic review will be on mild-to-moderate CD; while severe CD is implicated in greater morbidity and complications, mild-to-moderate CD affects a broader population of CD patients. Early intervention and management for this population may help reduce disease progression and associated healthcare costs [6].

Though 5-aminosalicylic acid (5-ASA) is widely used to treat mild-moderate CD, there exists little evidence that this treatment is effective [7]. Sulfasalazine may have a role for mild-moderate CD patients with colonic involvement [8]. Budesonide is recommended for the treatment of mild-

moderate CD per guidelines, but only for induction and not for maintenance [8]. As such, there are limited treatment options for individuals with mild to moderate CD [5, 7]. As an alternative for CD patients, traditional Chinese medicine (TCM) is a traditional form of medicine that uses various psychological (meditation) and physical approaches (acupuncture, herbs, and moxibustion) to address various health conditions [9]. Therapeutic herbal practices such as Tripterygium wilfordii Hook F (TwHF), moxibustion, and Fufangkushen colon-coated capsule (FCC) are emerging as options from TCM to aid in the mitigation of IBD symptoms [10-12]. Thus, TCM may be a potential strategy to manage clinical symptoms for patients with mild to moderate CD [9, 13].

Despite the prevalence of CD, there is a lack of literature focused on available alternative treatments besides established medications. As such, this systematic review and meta-analysis aimed to compile research on TCM to determine its efficacy for CD symptom relief, severity, and treatment for patients with mild to moderate CD compared to patients who receive no treatment [7, 13]. Although TCM is not a first-line therapeutic measure, the results could demonstrate the value of considering TCM as symptomatic management of mild to moderate CD [4, 5, 13].

METHODS

Review Protocol

Prior to conducting this systematic review, we wrote a study protocol outlining our planned approach for the identification and selection of relevant studies. We used the Cochrane Handbook's standard methodology for the analysis and followed the recommended PRISMA guidelines for reporting our methods and findings [14, 15]. Our original protocol is available upon request, and a log of changes made to the protocol once we initiated our formal review process can be found in the Supplementary file.

Study Eligibility Criteria

Traditional Chinese medicine encompasses a variety of practices such as traditional Chinese herbs, moxibustion, cupping, and acupuncture of all doses, frequency, and regimens [16, 17]. We included randomized controlled trials (RCTs) studying the effectiveness of TCM versus no treatment (placebo) at reducing symptom severity in mild to moderate CD patients. Participants of any age with mild to moderate CD were eligible for this review. Mild to moderate CD is defined as a Crohn's Disease Activity Index (CDAI) of 151-350 and a Crohn's Disease Endoscopic Index of Severity (CDEIS) of 3-12 [18-20]. Our inclusion criteria table with explanations can be found in the Supplementary file.

Primary Outcome Measure

Our primary outcome was changes in objective measures of CD activity as measured by CDAI and CDEIS. We defined our outcome as either change from baseline to post-treatment/follow-up or mean difference post-treatment/follow-up (mean ± standard deviation) [19-21].

Secondary Outcome Measure

Our secondary outcomes were changes in subjective measures of CD activity and changes in inflammation. We defined "change in subjective measures of CD" as measurements of self-reported pain or quality of life. Subjective assessments of symptoms are correlated to symptom improvements, as patients with CD symptoms are shown to have a decreased quality of life and an increase in pain [22-27]. We defined inflammation change as measurements of C-reactive protein plasma levels, tumor necrosis factor, interleukin expression, erythrocyte sedimentation rate, α1-acid glycoprotein, mucosal inflammation, or inflammatory mRNA expression [22-27]. Crohn's disease is characterized by inflammation mainly in the gastrointestinal tract, with symptom severity, specifically pain, being related to higher inflammation levels [19, 22-27].

Search Methods

Databases, search terms, limits

With the help of a research librarian, we searched MEDLINE via PubMed, the Cochrane Library via CENTRAL and CDSR, Scopus, and CINAHL for published articles from database inception to January 23, 2023 that addressed our research study question. No search limits were applied. We generated lists of MeSH terms and keywords to encompass our research themes of traditional Chinese medicine and Crohn's Disease. Next, we combined the result sets of these themes using the "AND" boolean function to find relevant studies. We used Cochrane's highly sensitive search strategy for identifying RCTs in MEDLINE, and applied it to other database searches [14]. Search strategies for each database are provided in the Supplementary file.

Additional search methods

We manually reviewed the reference lists for each study we found using Web of Science. We also used Google Scholar as an additional source of studies. This method expanded the number of RCTs we could review which we had to capture using MeSH-based searches. We also searched clinicaltrials.gov for any unpublished data. The details of our electronic search strategy are outlined in the Supplementary file.

Study Selection

Citations gathered from the search were encoded in Rayyan and included and excluded independently by all four team members [28]. The eligibility of each potential study was assessed by at least two non-expert reviewers independently and in duplicate. Studies found in Mandarin were reviewed by a single fluent investigator for eligibility. In this process, the titles and abstracts of potentially eligible studies were screened. After this initial review, full-text articles of potentially eligible studies were assessed by two of the reviewers independently and in duplicate. At this time, determinations were made regarding the appropriateness of each potential study for inclusion. Throughout this study selection, discrepancies were resolved among the reviewers and by a third reviewer through discussion.

Data Collection

Two non-blinded, independent reviewers extracted data using a standardized, piloted data collection form for

all studies meeting inclusion criteria. For each study, we determined the following information, if provided: methods, patient demographics, outcome measures, interventions, results, follow-up, and risk of bias. Reviewers resolved data discrepancies through discussions with a third non-blinded reviewer. We attempted to obtain missing data by contacting authors through email. A copy of the data collection form is in Supplementary file.

Assessment of Methodological Quality

Team members independently assessed the quality and bias of each article using the Cochrane's Risk of Bias 2 (RoB2) tool shown in Supplementary file [29]. Using the RoB2 tool, team members assessed five domains of bias, assigning judgment of "low risk of bias," "some concerns for bias," or "high risk of bias." Weighing these assessments of each domain of bias, an overall risk of bias was assigned to each article. In the case of discrepancies, the assessment results were discussed until an agreement was reached.

Analyses

Measure of Treatment Effect

For measures of objective and subjective change in CD severity and change in inflammation, mean differences were used to quantitatively evaluate the effects of TCM on CD. A formal narrative synthesis was used to analyze other details and outcomes.

Dealing with Missing Data

For studies that could not provide particular data, we contacted the authors via email. Additionally, we estimated data reported only in figures using the WebPlotDigitizer [30]. If complete data could not be gathered from the eligible studies because we received no response from the authors, or if data was insufficient, then the study was excluded from our meta-analysis and qualitative analysis. In addition, to calculate mean and SDs not reported, we used the Cochrane Handbook's recommended data conversion formula for variance measures [14, 31].

Data Synthesis

We opted for a random-effects model to analyze pooled data on CD symptom severity based on the assumption that the individual studies were estimating a range of intervention effects [14]. We used RevMan version 5.4 to complete the data synthesis [14]. Qualitative summarization was used in cases where outcomes could not be meta-analyzed. Lastly, we generated a summary assessment and categorized outcomes as favoring TCM, no treatment, neither treatment, or unclear.

Assessment of Heterogeneity

We used RevMan to conduct chi-square tests and generate an I^2 statistic, which informs whether the variation between our included studies are due to heterogeneity rather than chance.[14] Based on this data, we determined whether or not to combine study results for our primary outcome of interest. We used a p-value on the chi-square test of less than 0.10 to indicate statistically significant heterogeneity. If heterogeneity was present, we evaluated what screening criteria and methodological flaws may have produced this heterogeneity [14]. We then performed a sensitivity analysis to determine the largest number of homogeneous studies ($p>0.10$). In addition to this quantitative approach, we qualitatively identified any outliers.

Assessment of Reporting Biases

Using RevMan, we created a funnel plot for studies that reported only for our primary outcome via CDAI to assess for the presence of publication bias [14]. Using the funnel plot we visually evaluated whether a correlation existed between study sample size and effect size and if there was any visual asymmetry in the funnel plot.

Subgroup Analyses

We performed a subgroup analysis to determine whether concomitant medication use (i.e. corticosteroids) affected the CDAI primary outcome.

Sensitivity Analyses

A sensitivity analysis was performed based on all elements of our methodological quality (or "risk of bias") assessment: the Cochrane's Risk of Bias 2 (RoB2) tool [29]. We completed a sensitivity analysis for studies by excluding studies with medium or high risk of bias. Additionally, we performed a sensitivity analysis on studies that rely on WebPlotDigitizer to extract missing raw data.

RESULTS

Description of Studies

We retrieved 232 articles from our database searches and 0 from additional search methods, removing 62 duplicates. After screening the titles and abstracts of the remaining 170 records, we had 10 articles for full-text review. From this, we reviewed the full text of the 10 articles and assessed their study inclusion eligibility. This resulted in five papers being included in the review (Fig. 1). Five studies were excluded due to the unavailability of full-text or incorrect study design or outcome [32-36]. These studies are detailed in the Supplementary file.

Included Studies

The general characteristics of the five studies included in this review can be found in Table I [19, 37-40]. All five studies were randomized controlled trials published between 2014 and 2022. Four were located in China and one in Germany [19, 37-40]. Studies included 292 patients, ranging from 20 to 92 per individual paper[19, 37-40]. Four studies utilized interventions that were completed over 12 weeks (totaling 36 sessions), [19, 38-40], while one was held over four weeks (totaling 10 sessions) [37]. Most studies excluded subjects on immunosuppressants and steroid-like mesalamine [33, 37, 38]. Three studies included only CDAI as their primary outcome [37-39], while two studies included both CDEIS and CDAI [19, 40]. Secondary outcomes were investigated in all five studies [19, 37-40]. Two studies tracked changes in participants' subjective measure of CD severity (IBDQ, Inflammatory Bowel Disease Questionnaire) [19, 37], and all five studies monitored changes in inflammatory biomarkers [19, 37-40].

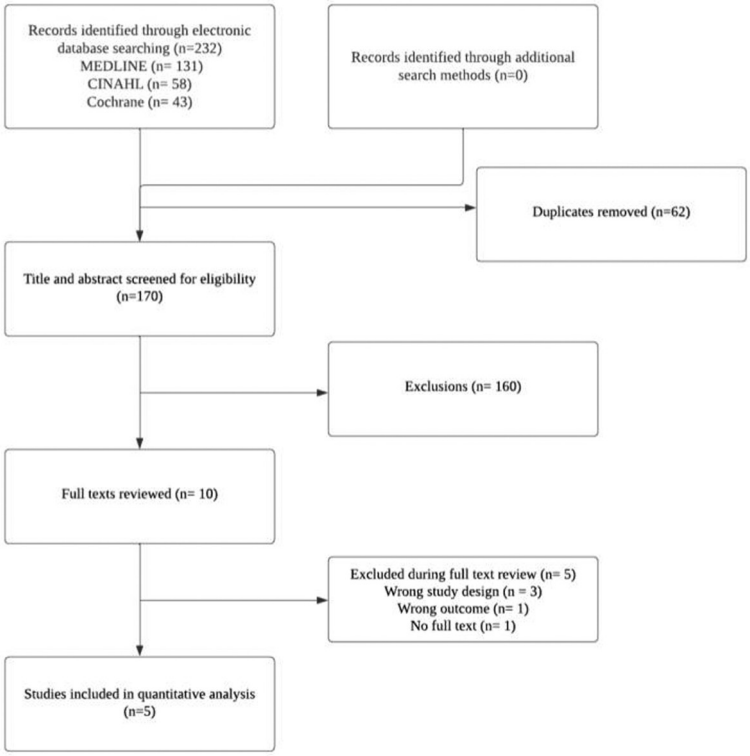

Fig. 1. Study Selection PRISMA Flow Diagram.

Table I. General study characteristics of included studies

Authors (year published), reference	Location (country)	Study design	Number of patients (n); diagnostic criteria	Control	Interventions	Concomitant medications
Bao CH, (2014), [19]	China	RCT	92 patients; CDAI 150-350	Wheat bran-partitioned moxibustion combined with superficial acupuncture (n=46)	Herb-partitioned moxibustion combined with acupuncture (n=46)	None
Joos S, (2014), [37]	Germany	RCT	51 patients; CDAI 150-350; confirmed with an endoscopic biopsy in the past 2 years	Minimal acupuncture placed away from the classical or trigger points (non-acupoints) and inserted only 1–2 mm deep without manipulation. (n=24)	Acupuncture and moxibustion (n=27)	None
Zhao C, (2015), [38]	China	RCT	20 patients; CDAI 150-350	Wheat-bran-partitioned moxibustion combined with superficial needle puncture at non-meridian, non-acupoint sites (n=10)	Herb-partitioned moxibustion combined with acupuncture (n=10)	Patients either (1) took no medication or (2) took only salicylates and/or prednisone (dose ≤ 15 mg treatment lasting at least one month); no use of immunosuppressants or biologics within the past 3 months.
Guo S, (2022), [39]	China	RCT	63 patients; CDAI 150-350	Moxibustion with Placebo acupuncture (n=32)	Moxibustion controlled at 43^0C combined with acupuncture (n=31)	No drugs except for prednisone 15 mg/d, azathioprine 1 mg/kg per day, methotrexate 15 mg each week, or mesalazine 4 g per day
Bao C, (2022), [40]	China	RCT	66 patients; CDAI 150-350; additionally confirmed ileocolonoscopy and histopathology	Sham acupuncture and sham moxibustion (n=33)	Acupuncture and moxibustion (n=33)	Not taking medicine or one or more of the following: Prednisone ≤15 mg/d (at least for 1 month); azathioprine (≤1 mg/kg/d), methotrexate (≤15 mg/wk), or mesalazine (≤4 g/d) (at least for 3 months);

CD: Crohn's disease; RCT: randomized controlled trial.

Characteristics of Included Interventions

All five included studies involved the use of herb-partitioned moxibustion combined with acupuncture (Supplementary file) [19, 37-40]. A detailed diagram of the acupuncture and moxibustion points can be seen in Fig. 2. Of the five interventions using acupuncture, four inserted the needle 20-30 mm into the skin for 30 min [19, 38-40] and one 5-30 mm for 30 min [37]. The composition of moxibustion varied or is unknown in some studies; however, a majority contained the following main ingredients: Coptis chinensis, Radix Aconiti Lateralis, Cortex Cinnamomi, Radix Aucklandiae, Flos carthami, Salvia miltiorrhiza, and Angelica sinensis [19, 37-40].

Risk of Bias of Included Studies

As seen in Table II, of the five studies included in this review, all five were determined to be "low risk," no studies were determined to have "some concerns," and no studies were determined to be "high risk" [19, 29, 37-40]. Almost all studies were determined to be "low risk" for each domain of bias [19, 29, 37-40]. However, for "Domain 3: Outcome Data," two studies were determined to have "some concerns" [29, 37, 38]. Because "some concerns" was only associated with one domain of bias for each of the two identified studies, this did not impact the overall risk of bias from still being determined to be "low risk" [19, 29, 37-40]

Primary Outcome

All five studies measured CDAI scores [19, 37-40]. The results of these CDAI measurements in each study are provided in Supplementary file. There was an overall difference in mean CDAI decrease between the TCM intervention group and the placebo control of -49.91 (95%CI: -64.97 - -34.84; p<0.00001, Fig. 3) [19, 37-40]. There was moderate study heterogeneity (I^2=61%, p=0.03) [19, 37-40].

Two studies measured CDEIS [19, 40]. The results of these CDEIS measurements in each study are provided in the Supplementary file. The overall difference in mean CDEIS decrease between the TCM intervention group and the placebo control was -2.96 (95%CI: -6.3 - 0.40; p=0.08, Fig. 3)[19, 40] There was moderate study heterogeneity (I^2=53%, p=0.14). For this primary outcome, no sensitivity analyses were performed [19, 40].

Secondary Outcome

Two studies measured IBDQ scores for both the treatment and control groups [19, 37]. For this measure, higher scores (and positive mean differences) represent better quality of life (QoL) [19, 37]. As seen in Table III, positive IBDQ mean differences were observed for both the treatment and control groups in each study [19, 37]. The positive IBDQ mean differences of the treatment groups were greater than those of the control groups in each study [19, 37].

Each of the five included studies measured changes in inflammatory biomarkers [19, 37-40]. A complete list of these measurements is provided in Table III [19, 37-40]. Overall, the changes in inflammatory markers across the studies were mixed. Three studies included C-reactive protein (CRP) measurements (mg/L) [19, 37-40]. Two of these studies reported the mean difference (change from baseline to second measurement) of these CRP measurements for each group [19, 37]. Although the mean CRP difference detected by Bao et al. 2014 was lower in the treatment group than the control group [19], the mean CRP difference was higher in the treatment group than the control group in Joos S et al., 2004 [37]. However, it is notable that the time when CRP

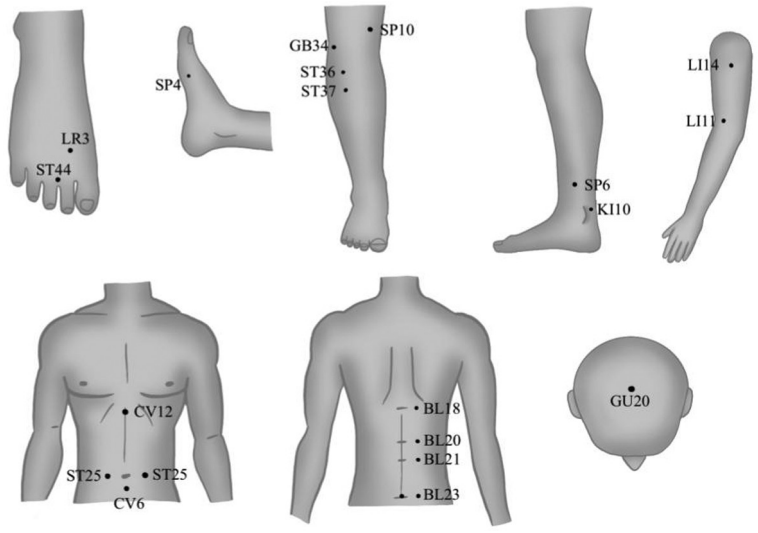

Fig. 2. A diagram demonstrating the acupuncture and moxibustion points used across the included studies (LR= liver, ST=stomach, SP= spleen, GB= gallbladder, KI=kidney, LI= large intestine, CV= conception vessel, BL=bladder, GV= governor vessel). LR3, ST36, SP6, CV12, and ST25 were used by all five studies.19,37–40 SP4, ST37, KI3 were used by four studies.19,38–40 BL18-BL23, ST44, SP10, GB34, and GV20 were exclusively used by one paper.37 LI14 was cited by two papers.39,40 LI11 was used in three papers.37,38,40 CV6 was exclusively used as a point for moxibustion by three of the five papers.19,37,38

Table II. Methodological Quality Assessment

Authors (Year Published)	Domain 1: Randomization	Domain 2: Intervention	Domain 3: Outcome Data	Domain 4: Bias in Measurement	Domain 5: Bias in Outcome	Overall Risk of Bias
Bao C, (2014), [19]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Joos S, (2004), [37]	Low Risk	Low Risk	Some Risk	Low Risk	Low Risk	Low Risk
Zhao C, (2015), [38]	Low Risk	Low Risk	Some Risk	Low Risk	Low Risk	Low Risk
Guo S, (2022), [39]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bao C, (2022), [40]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Table is utilized to assess risk of bias in randomized trials included in Cochrane Reviews [29]. Risk of Bias 2 is structured into 5 domains of bias, each of which focuses on a different aspect of trial design, conduct, and reporting.19 Judgments can be "Low Risk of bias," "Some Risk of bias," or "High Risk of bias" [29].

was measured varied between these studies, as one measured CRP at 12 weeks from baseline (post-treatment) [19] and the other study measured CRP at 4 weeks from baseline [37]. The third study which evaluated CRP measurements did not provide mean differences for the treatment and control groups [40]. Instead, the difference in mean change from baseline to post-treatment of the treatment group compared to the control group was provided [40]. Because the individual mean differences associated with the treatment and control groups were not provided, it is not possible to discern whether one group experienced greater CRP measurement reduction from this result [40].

Subgroup Analysis by Concomitant Medication Use

Among the five studies, three studies involved patient populations that utilized corticosteroids or immunosuppressants concurrently [38-40], while two involved patients that did not [19-37]. Of note, patients taking concomitant medications were not using biologics [38-40]. We performed a subgroup analysis to determine whether concomitant medication use affected the outcome. For studies with concomitant and non-concomitant medication use, the difference in mean CDAI decrease between TCM intervention group and placebo control was -45.39 (95%CI: -51.76, -39.02) and -52.37 (95%CI: -98.65, -6.09), respectively (Fig. 4) [38-40]. The subgroup analysis demonstrates that the difference in mean CDAI decrease between TCM intervention group and placebo control was similar between patients that did and did not have concomitant medication use [38-40].

Sensitivity Analyses

Sensitivity analysis was completed to examine whether or not data extraction by WebPlotDigitizer had any bearing on the results [30]. We used the figures from Zhao et al. [38], to extract the data on CDAI for both the TCM intervention and placebo group. After excluding this study, the pooled estimate for the mean CDAI decrease between TCM intervention group and placebo control was -47.47 (95% CI: -63.59, -31.34) (Supplementary file) [19, 37, 39, 40]. Therefore, our overall results were not sensitive to the use of WebPlotDigitizer for Zhao et al. [30, 38].

Publication Bias

For this random-effects model on CDAI, we generated a funnel plot despite the small number of studies (<10), (Appendix 10) [19, 37-40]. Included eligible studies sometimes produced non-significant results in certain areas, reducing the possibility of publication bias [19, 37-40]. The figure demonstrates no evident risk of publication bias for this outcome.

DISCUSSION

Traditional Chinese medicine has a long history of treating gastrointestinal diseases, but its effectiveness is often disputed [41]. This systematic review demonstrates that TCM may be an effective treatment for patients with mild to moderately active CD. A meta-analysis of five studies indicated that TCM significantly reduced CDAI over a 12-week treatment period compared to the placebo group [19, 37-40].

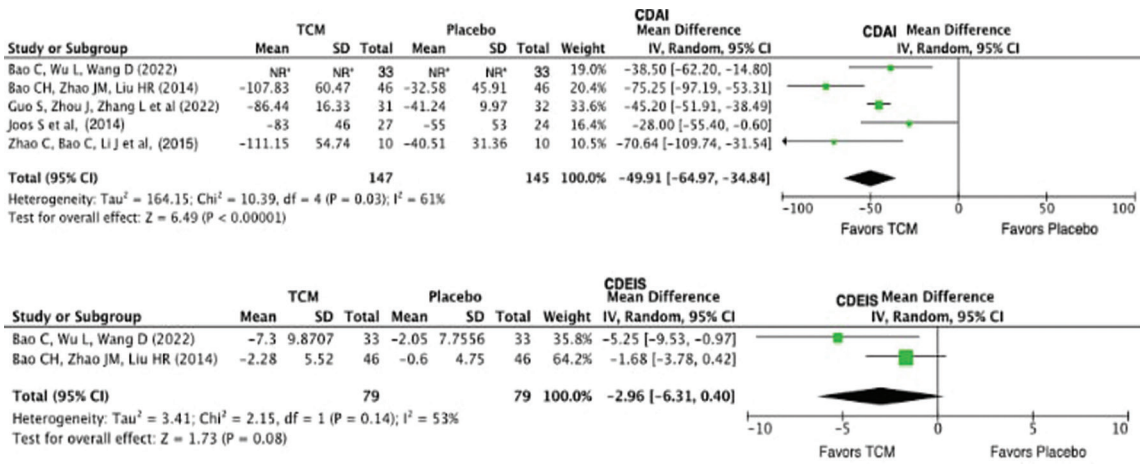

Fig. 3. Forest plots of TCM treatment on Crohn's disease severity using CDAI (top) and CDEIS (bottom).

Table III. Results for secondary outcomes: measurements of QoL and changes in inflammation with intervention and control mean difference

Author, (year published), reference	Measurement tool or method used	When measured	Intervention mean difference (change from baseline to post-treatment) (mean ± SD)	Control mean difference (change from baseline to post-treatment) (mean ± SD)
Bao C., (2014), [19]	QoL Survey (IBDQ)	12 Weeks	24.56 ± 34.15	9.93 ± 19.13
Joos S (2004), [37]	QoL Survey (IBDQ)	4 weeks	41 ± 19	30 ± 22
Bao C, (2014) [19]	Laboratory Tests (HGB, CRP, and ESR levels)	12 Weeks	HGB (g/L): 5.09 ± 14.45 ESR (mm/h): -3.77 ± 13.00 CRP (mg/L): -8.67 ± 20.04	HGB (g/L): -0.93 ± 10.07 ESR (mm/h): -0.21 ± 10.12 CRP (mg/L): 1.16 ± 12.11
Joos S, (2004), [37]	Laboratory tests (a-GP, CRP)	4 weeks	a-GP: -7.7 ± 19.5 CRP: 0.3 ± 1.4	a-GP: -3.8 ± 20.5 CRP: -0.2 ± 0.6
Zhao C, (2015), [38]	Laboratory results (FOXP3 and Treg cells, Ratio of Th17/Treg RORγt protein)*	12 weeks	Th17/Treg ratio: -1.757 ± 0.412 IL-17: -552.27 ± 82.90 IL-17 mRNA: -0.018 ± 0.0027 RORγt:-742.8 ± 130.6 RORγt mRNA: -0.066 ± 0.00913 FOXP3: 561.3 ± 227.1 FOXP3 mRNA:0.010± 0.00082	Th17/Treg ratio: -0.943 ± 0.209 IL-17: -187.34 ± 48.39 IL-17 mRNA: -0.00794 ± 0.00278 RORγt: 139.3 ± 188.8 RORγt mRNA: -0.014 ± 0.0086 FOXP3: -87.31± 200.62 FOXP3 mRNA: 0.001± 0.00057
Guo S, (2022) [39]	Expression Levels of TGF-β1, TβR1, TβR2, Smad3, and Snail Proteins in Intestinal Epithelial Tissues, Expression of E-cadherin and Fibronectin in Intestinal Epithelial Tissues*	12 Weeks	TGF-β1: -16575 ± 3425.5 TβR1: -2607 ± 1117.1 TβR2: -16239 ± 2475.2 Smad3: -10907 ± 2051.0 Snail: -6818 ± 737.1 E-cadherin: 8610 ± 1019.1 Fibronectin: -20197 ± 2014.7	TGF-β1: -4199 ± 3736.8 TβR1: -824 ± 910.4 TβR2: -14871 ± 2932.6 Smad3: -10548 ± 2636.8 Snail: -2530 ± 715.5 E-cadherin: 3631 ± 623.0 Fibronectin: -10039 ± 1775.3
Bao C, (2022), [40]	CRP	12 weeks	-7.4 (95% CI: 0.8 - 13.9, p = 0.028) difference in mean change from baseline of the treatment group compared to control group	N/A
Bao C, (2022), [40]	IFN-γ TNF-α IL-1β IL-17A IL-23	Unknown	IFN-γ difference: 8.1 (95%CI: 2.3–13.9) TNF-α difference: 16.2 (95% CI: 0.4–32.1) IL-1β difference: 5.5 (95% CI: 0.2–10.8) IL-17A difference: 7.2 (95% CI: 3.0–11.4) IL-23 difference: 16.3 (95% CI: 1.8–30.7) difference in mean change from baseline of the treatment group compared to control group	N/A

CD: Crohn's disease; CDAI: Crohn's Disease Activity Index Score; HGB: hemoglobin; ESR: erythrocyte sedimentation rate; a-GP: α1-acid glycoprotein; CRP: C-reactive protein; SD: standard deviation; CI: confidence interval; IBDQ: inflammatory bowel disease questionnaire; QOL: quality of life. *Calculated through WebPlotDigitizer, as raw data was not available.

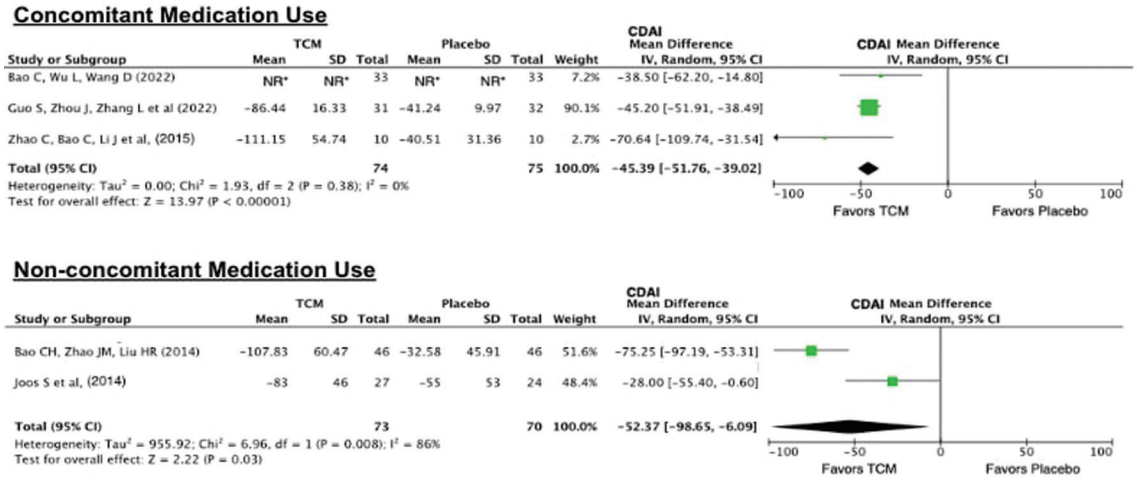

Fig. 4. Forest plots for subgroup analysis of studies by concomitant medication use (top) and non-concomitant medication use (bottom).

Only two studies reported CDEIS and did not demonstrate a statistically significant difference in CDEIS reduction between the two groups [19, 40] There was significant heterogeneity in measures of our secondary outcome between the studies [19, 37-40]. In narrative synthesis, we found mixed results regarding CRP [19, 37-40]. Lastly, two studies showed a greater improvement in QoL for the intervention group [19-37].

When judging the external validity of this review, it was noted that four of the five included studies were conducted within China [19, 37-40]. Due to this similarity in study setting (and therefore population), external validity could be increased by replicating studies meeting similar inclusion criteria in other populations.

The included studies did not investigate TCM comprehensively; for example, they did not capture practices such as cupping or oral herbal treatments. As such, further investigation is warranted, utilizing study designs that meet inclusion criteria similar to those outlined within this review. Additional studies that investigate the effects of TCM on patients who are on concurrent medications are particularly necessary, as this may provide a more realistic picture of the true benefits of TCM and Western medicine when used in conjunction with each other. Lastly, current guidelines define mild to moderate CD with a CDAI of 150-220 [41, 42]. However, the included studies used the 150-350 range for their inclusion criteria.

The RCT study design in each of the included studies provide further confidence in the observed consistency of results [19, 37-40]. All of the studies included a relatively small sample of participants [19, 37-40]. Although the results were consistent across these studies, incorporating study designs with larger sample sizes could enhance the validity of these results and allow for results to apply to increased patient populations. When considering the factors contributing to the methodological quality of the included studies and the consistency of the identified results, it was determined that the results of this review have strong internal validity [19, 37-40].

This review followed Cochrane's guidelines to ensure the methodology was robust [14]. The scope of the systematic review was clearly outlined and followed, with predefined inclusion criteria for study design, population, intervention, exposure, comparison condition, and outcome. In addition, a comprehensive literature search was conducted, with a predefined search strategy and no language restrictions applied throughout multiple databases. The search strategy follows the requirements of the PRISMA guidelines [24]. Two independent reviewers validated the study selection using a data collection form and the Cochrane risk of bias tool for RCTs [14, 29] Disagreements were resolved through the discussion of the two reviewers or a consensus with a third investigator. Language may have limited the search strategy and results of this literature search. Additionally, the possibility of inaccurate treatment effects should be considered due to the number of studies included in the review and the sample size of the studies. With only five included studies with small participant pools, it is difficult to generalize the results of these RCTs to a broader population. An assessment of a subgroup analysis occurred due to three of the five studies involving patients taking corticosteroids or aminosalicylates concurrently [38-40]. Although the analysis demonstrated that the difference in mean CDAI was similar between patients that did and did not have concomitant medication use, the possibility of its influence on the outcomes should not be dismissed [38-40]. Across the studies, many different metrics were used to measure inflammatory markers. Three studies reported CRP, but TCM treatment did not yield any apparent effect for these studies [19, 37, 30] Two studies reported a more positive effect on QoL scores in the treatment group compared to control [19, 37]. More studies reporting inflammatory biomarkers and QoL scores can make these relationships clearer. Lastly, it is worth noting that while all studies used acupuncture and moxibustion for TCM treatment, there was some variability in selected pressure points and study length that may have affected results.

Our findings align with a similar review by Xie et al. [44], which investigated the effect of acupuncture and moxibustion on patients with CD. Both reviews demonstrated the effectiveness of TCM treatment in reducing CD symptoms. However, our review differed in a few important ways. The studies included in our analysis required a placebo control group instead of an anti-inflammatory agent comparison [44]. The comparison of TCM to a placebo group more clearly elucidates the impact of TCM treatment on baseline CD symptoms. Additionally, Xie et al. did not conduct a meta-analysis for the CDAI outcome; our paper demonstrated a statistically significant difference in CDAI reduction between the TCM and placebo groups [44]. Similarly, another review by Ji et al. [45] compared the efficacy of acupuncture and moxibustion to oral sulfasalazine in treatment of IBD, which found TCM to be more effective. In contrast, this review aimed to identify TCM's effects versus a placebo for mild to moderate CD patients.

Given the results from this systematic review, patients with mild to moderate CD may benefit from TCM in reducing symptom severity. However, this data is only preliminary and requires further investigation, as the included studies had some risk of bias and were moderately heterogeneous. Furthermore, the number of studies included was rather small, at five papers. Future research could explore a comparison of TCM's effectiveness to other existing treatments for mild to moderate CD, including other methodologies of TCM such as cupping or *qigong*. Conversations between physicians and CD patients exploring TCM treatment alternatives may facilitate better outcomes and care.

More research is needed to determine if TCM truly benefits patients with mild to moderately active CD. Current, existing studies are generally small and include ethnically homogenous participants. More high-quality studies with larger participant pools in different global populations are necessary to determine the true efficacy and applicability of TCM to larger populations.

CONCLUSIONS

The studies included in this systematic review and meta-analysis suggest that TCM, namely acupuncture and moxibustion, may provide benefit for mild to moderate CD symptoms. Despite the mixed effect that acupuncture and moxibustion appeared to have on inflammatory biomarkers, data in our included studies found that the combination of

acupuncture and moxibustion may reduce CDAI and CDEIS scores in patients with mild to moderate CD.

Conflicts of interest: C.A.S. has served as a consultant for Abbvie, BMS, Boomerang, Buhlmann, Janssen, Lilly, Napo, Pfizer, Prometheus Biosciences & Labs, Roivant, Takeda, and Trellus Health; received grants from Abbvie, Janssen, Pfizer, and Takeda; and is co-founder of MiTest Health, LLC, technology "System and Method of Communicating Predicted Medical Outcomes" licensed to Takeda. M.L.C., K.L.M., R.R.C., W.A.C., R.W.Y., M.A.Y. have no conflicts of interest to disclose.

Authors' contribution: This project was conceptualized by K.L.M. It was written by M.L.C., K.L.M., R.R.C., and W.A.C.. Data was collected by M.L.C., K.L.M., R.R.C., and W.A.C. and visualized by M.L.C.. Illustrations were done by K.L.M.. M.L.C., K.L.M., R.R.C., W.A.C., M.A.Y., R.W.Y., and C.A.S.. All authors have read and agreed to the published version of the manuscript.

Acknowledgements: We would like to thank librarian Heather B. Blunt for helping us with database searching and website navigation.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/ 10.15403/jgld-5729

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