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Original Article

Effect of Chinese Herbs on Chronic Pain through Liver Meridian Entry

Chen-Pi Li[1,2], Jui-Ting Yu[3], Ying-Jui Ho[4,5], Ming-Ling Yang, MS[6,7], Wen-Chieh Liao[6,7,8], To-Jung Tseng[6,7], and Ru-Yin Tsai[6,7*]

[1] Nurse Practitioner, Tung's Taichung MetroHarbor Hospital, Taichung City, Taiwan
[2] Department of Public Healthy, Chung Shan Medical University, Taichung City, Taiwan
[3] Tung's Taichung MetroHarbor Hospital, Division of Hematology/Medical Oncology, Taichung City, Taiwan
[4] Department of Psychology, Faculty of Medicine, Chung Shan Medical University, Taichung City, Taiwan
[5] Clinical Psychological Room, Chung Shan Medical University Hospital, Taiwan Taichung City, Taiwan
[6] Department of Anatomy, School of Medicine, Chung Shan Medical University, Taichung City, Taiwan
[7] Department of Medical Education, Chung Shan Medical University Hospital, Taichung City, Taiwan
[8] Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung City, Taiwan

Purpose: Despite their wide use in clinical practice, Chinese herbs remain a controversial treatment for chronic pain. Our objective was to provide an updated meta-analysis to determine the effect size of Chinese herbs on chronic pain conditions.
Method: A systematic literature review and meta-analysis was performed.
Results: Five databases (PubMed, SDOL, EBSCO, ProQuest, and OVID) were queried for studies published between January 2010 and December 2021. Only randomized controlled trials (RCTs) of Chinese herb intervention for people with chronic pain were included. This meta-analysis included six RCTs, comprising 839 participants in total. Chronic pain was significantly improved by Chinese herbs in the administration by bathing, rectal suppositories, or oral groups, especially for herbs whose therapeutic action is via the liver meridian entry.
Conclusion: This meta-analysis suggests that Chinese herbs are an effective intervention for people with chronic pain. They may be considered as an adjuvant in clinical chronic pain management for patients needing long-term anti-analgesic drug treatment or with neuropathic pain.

Keywords: Chinese herb; liver meridian entry; chronic pain; neuropathy; and neuropathic pain.

1. Introduction

Chronic pain is a major and common health problem worldwide and can be due to a wide variety of factors. Chronic pain has a significant impact on society and individuals[1]. Chronic pain is a long-term condition that requires special treatment and care, and most patients with chronic pain receive multimodal treatment. Although there are treatment options available, none are universally endorsed, and patients must weigh the benefits against the side effects of each [2]. A study reported that patients frequently used complementary therapies, with the most common being chiropractic, acupuncture,

* Corresponding Author: Ru-Yin Tsai
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: +886-4-24730022 ext. 11613
E-mail: iris8084@gmail.com

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and herbalism[3,4]. However, there is a lack of evidence for the effectiveness of Chinese herbs. Herbal medications have shown potential for safe and effective management of chronic pain[5-7], and reports have suggested that Chinese herbs may offer a supplementary or alternative method for effective and safe treatment. In traditional Chinese medicine, the human body is regarded as an organic whole, with every part intertwined via collaterals and meridians[8]. The meridian refers to the therapeutic effects of a Chinese herb on some part of the body; a Chinese herb might elicit evident therapeutic action on the physiological or pathological changes on one or several meridian entries[8]. This study is the first assessment of Chinese herb treatment on the antinociceptive effect of chronic pain potentially regulated via the liver meridian entry.

2. Materials and methods

2.1. Data sources and searches

To examine the effects of Chinese herbs on chronic pain, RTCs were queried from PubMed, SDOL, EBSCO, ProQuest, and OVID (January 2010 to DEC 2021). The keywords consisted of "Chinese herb," "herb," "chronic pain," "neuropathy," and "neuropathic pain." The search was limited to clinical trials with human subjects. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance was followed. Articles identified in this manner were retrieved, and their reference lists were searched for additional relevant articles.

2.2. Eligibility criteria

Studies were included if (a) participants were diagnosed with chronic pain or neuropathic pain; (b) the intervention included Chinese herbs; (c) the outcome was measured on the VAS; and (d) studies were described as RCTs and were in English. Studies were excluded if they pertained to short-term effects and anthroposophic drugs or were conference proceedings, abstracts only, review articles, letters, discussions, and editorials.

2.3. Selection of studies

The data screening and selection process was performed independently by two authors (JTY and CPL) and was verified by a third author (RYT). A hard copy of all the articles was obtained and read in full. Details of the selection process are shown in the PRISMA flow diagram (Figure 1).

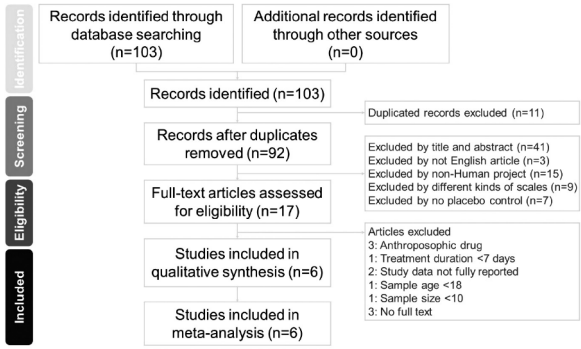


Figure 1. Diagram of the study selection process for the systematic review and meta-analysis.

2.4. Data extraction

Two authors (RYT and CPL) independently extracted data using a standardized data extraction form guided by the Cochrane Handbook[9]. The following data were extracted from the studies: the authors, year of publication, study design, sample size, participants' demographics, duration of the intervention, type(s) of Chinese herb(s), descriptions of the intervention group and control group, outcomes, and measurements.

2.5. Quality assessment

The Cochrane Risk of Bias (RoB 2.0) tool[10] was calculated for quality assessment of the included studies. A study was judged to be at high risk of bias overall if at least one domain showed a risk of bias.

2.6. Data analysis

The primary end point for this study was improvement in chronic pain management by administration of Chinese herbs. For each study, the SMD of the VAS between the intervention and placebo control groups was calculated. A random-effects model was employed to pool individual SMDs; all analyses were performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA). Between-trial heterogeneity was determined using the I^2 test, and values >50% were regarded as

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Table 1. Summary of randomized placebo-controlled trials of Chinese herbs for chronic pain.

Author, year	Patients' diagnosis	Enrolled sample number (Male/Female)	Average age, years	Intervention herb	Administration routes	Meridian entry	Dosage	Double-blind	Follow-up time (days)	Outcome measurement	Combined with other analgesic
Chrubasik S (2010)	Chronic soft tissue pain	Intervention: 140 (59/81) Placebo: 141 (48/93)	Intervention: 48.6 ± 13 Placebo: 48.9 ± 13	Capsaicin	Topical use	Heart and Spleen	Cream containing capsaicin 0.05%	Yes	21	VAS pain sum score	No
Liu X (2014)	Paraplegia spasticity	Intervention: 80 Placebo: 80	18 to 65 years old	Herba speranskiae tuberculatae 240 g, Spa. caulis 120 g, P. radix alba 120 g, C. fructus 120 g, A. sinensis radix 60 g, U. ramulus cum uncis 100 g	Bathing	Liver, Lung, Heart, Stomach, Renal, and Spleen	Herbs boiled in 50 L water and then transferred into a 500 L bath. Participants bathed for half an hour.	Yes	365	VAS, Spasm frequency, Sleep quality, and Skin allergy	Not mentioned
Srivastava S (2016)	Knee osteoarthritis	Intervention: 78 (25/53) Placebo: 82 (32/50)	Intervention: 50.23 ± 8.08 Placebo: 50.27 ± 8.63	Curcuma longa extract	Oral administration	Liver and Spleen	500 mg/day	Yes	120	VAS, WOMAC, and biomarkers (IL-1β, ROS, and MDA)	Diclofenac 50 mg/day
Morgia G (2017)	Chronic prostatitis / CPPS	Intervention: 24 Placebo: 24	Intervention: 32 Placebo: 32	Curcumina and Calendula	Rectal suppositories	Liver and Spleen	Curcumin extract 350 mg and Calendula extract 80 mg (1 suppository/die for 1 month)	Single-blinded	90	VAS, NIH-CPSI, IIEF-5,and PEDT	Not mentioned
Rich G (2017)	Functional dyspepsia	Intervention: 58 (24/34) Placebo: 56 (17/39)	Intervention: 46.6 ± 14.3 Placebo: 48.5 ± 14.3	Menthacarin	Oral administration	Liver and Lung	Menthacarin®, fixed combination of 90 mg peppermint oil (Mentha× piperita L.; WS® 1340) and 50 mg caraway oil (Carum carvi; WS® 1520) / capsule	Yes	28	VAS and NDI	Not mentioned
Salimzadeh A (2018)	Knee osteoarthritis	Intervention: 39 Placebo: 37	Intervention: 58.9 ± 7.5 Placebo: 58.5 ± 7.4	Garlic	Oral administration	Stomach, Lung, and Spleen	1000 mg / day	Yes	90	WOMAC and BMI	No

BMI: Body Mass Index; CPPS: Chronic Pelvic Pain Syndrome; IIEF-5: International Index of Erectile Function Questionnaire; IL-1β: Interleukin-1b; MDA: Malondialdehyde; NDI: Nepean Dyspepsia Index; NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index Score; PEDT: Premature Ejaculation Diagnostic Tool; ROS: Reactive Oxygen Species; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

considerable heterogeneity. Funnel plots and Egger's test were used to examine potential publication bias. Statistical significance was defined as p-values < 0.05, except for the determination of publication bias, which employed $p < 0.10$.

3. Result

3.1. Study search and characteristics of included patients

We retrieved 92 non-duplicate randomized controlled trial (RCT) citations for a review of their titles and abstracts and included 17 articles for meticulous evaluation after eliminating references violating the inclusion criteria (Figure 1). With further careful reading, 11 records were eliminated because of the use of anthroposophic drugs[11-13], the study data being not fully reported[14,15], the examination of pediatric subjects (<18 years old)[16], the unavailability of full text[17-19], a short treatment duration (<7 days)[20], and a small sample size (n < 10)[21]. As a result, six articles were included in this meta-analysis[22-27]. For the RCTs included in this study, five were double-blind[22-24,26,27] and one was single-blind[25]. The final quantitative analysis included 839 participants. The participant characteristics and study methodology are shown in Table 1.

3.2. Quality assessment

The risk of bias was moderate across five domains in the included trials, and all trials were limited in quality (Figures 2A and 2B). One study had a

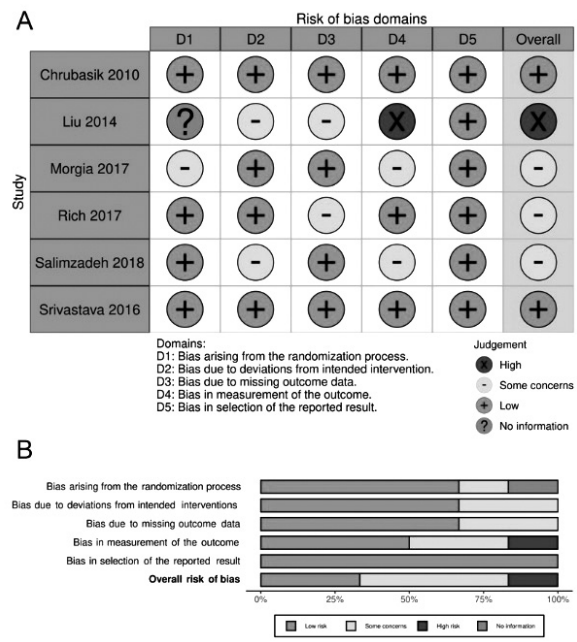


Figure 2. Assessment of methodological quality of the included trials. (A) Risk of bias for each included study. (B) The overall summary of bias of the 16 studies.

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possibility of bias due to its randomization process. Two studies had a high risk of bias due to their randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and the selection of the reported results.

3.3. Impact of Chinese herbs on chronic pain

The total standardized mean difference (SMD) of Chinese herbs versus placebo controls on pain was −1.67 (95% confidence interval (CI): −2.81 to −0.54) (Figure 3). Subgroup analyses were performed to explore the possible influence of study characteristics on these findings at the immediate post-intervention follow-up. We selected four variables to categorize the subgroups: administration route, meridian entry, lesion position, and length of treatment duration. The administration route analysis is shown in Figure 4A. The data show a significantly lower chronic pain level in those treated with Chinese herbs versus placebo controls in the bathing group (SMD: −4.71; 95% CI: −5.31 to −4.11) and rectal suppositories group (SMD: −2.82; 95% CI: −3.62 to −2.02), topical group (SMD: −0.80; 95% CI: −1.21 to −0.40), and oral administration group (SMD: −0.62; 5% CI: −1.28 to 0.03). Regarding SMD heterogeneity, the I^2 was 88.32% in the oral administration group. Specifically, the meridian entry analysis showed a significantly reduced chronic pain level in those treated with Chinese herbs versus placebo controls in the liver meridian entry group (SMD: −2.33; 95% CI: −4.02 to −0.65) compared to the non-liver meridian entry group (SMD: −0.39; 95% CI: −1.21 to 0.42). Regarding SMD heterogeneity, the I^2 was 97.997% in the liver meridian entry group and 85.992% in the non-liver meridian entry group (Figure 4B). The lesion position analysis showed a significantly decreased chronic pain level in those treated with Chinese herbs versus placebo controls in the non-knee osteoarthritis group (SMD: −2.38; 95% CI: −4.05 to −0.71) and slight effect in knee osteoarthritis group (SMD: −0.32; 95% CI: −0.97 to 0.32). Regarding SMD heterogeneity, the I^2 was 97.623% in the non-knee osteoarthritis group and 81.656% in the knee osteoarthritis group (Figure 4C). The length of treatment duration analysis showed a significantly suppressed chronic pain

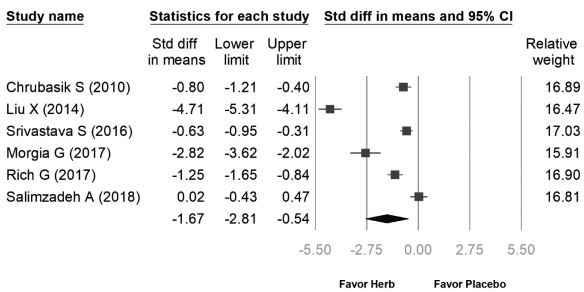


Figure 3. The overall effect of Chinese herbs on chronic pain measured by visual analog scale (VAS) was compared with placebo.

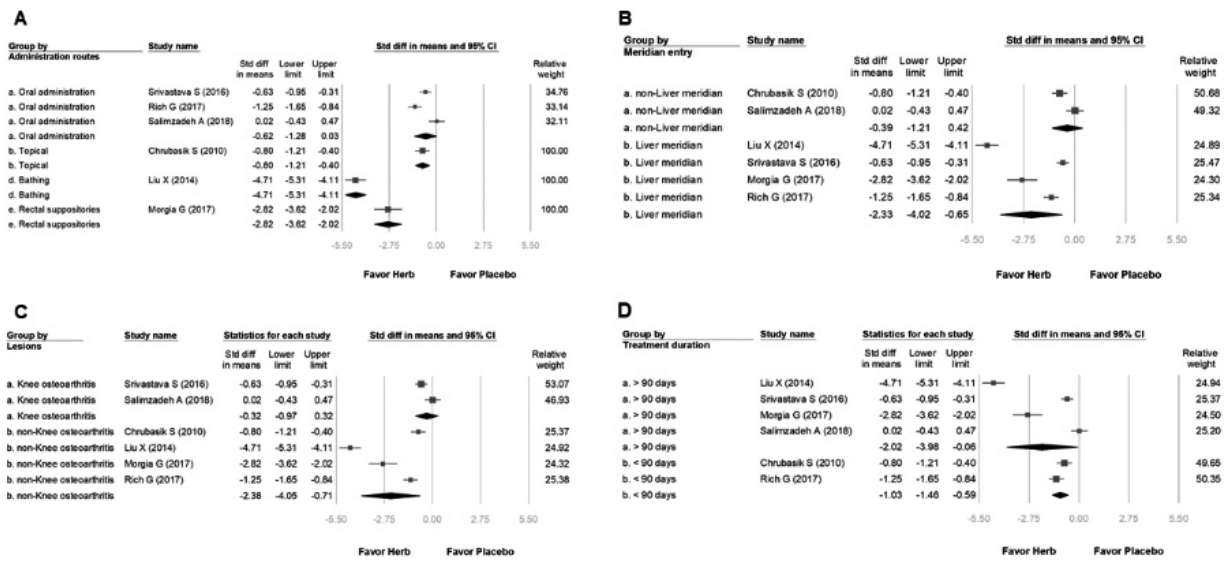


Figure 4. Subgroup analysis of effects of Chinese herbs on chronic pain. (A) administration route, (B) meridian entry, (C) lesion position, and (D) length of treatment duration.

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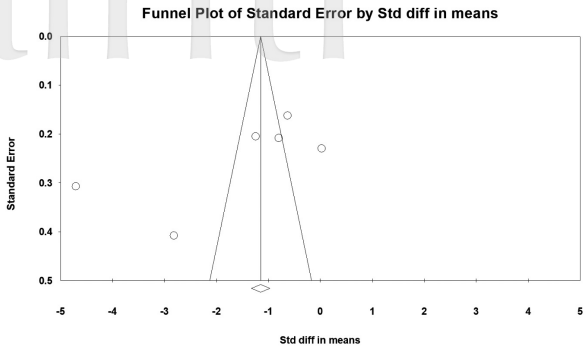


Figure 5. Funnel plot for studies reporting on Chinese herb treatments for chronic pain management compared with placebos.

level in patients given Chinese herbs versus placebo controls in both the >90 days of treatment group (SMD: −2.02; 95% CI: −3.98 to −0.06) and in the <90 days of treatment group (SMD: −1.03; 95% CI: −1.46 to −0.59). Regarding SMD heterogeneity, the I^2 was 98.396% in the >90 days of treatment group and 56.559% in the <90 days of treatment group (Figure 4D).

3.4. Publishing bias

The Egger's test indicated no significant publication bias regarding the overall SMD (p = 0.1349). The funnel plot for the SMD of chronic pain is shown in Figure 5.

4. Discussion

Chinese herbs have been widely studied as treatments for various chronic pain symptoms in both animal and human studies, but their clinical efficacy remains unclear. This meta-analysis demonstrated four administration routes of Chinese herbs in treating chronic pain: oral administration, subcutaneous injection, bathing, and rectal suppositories. All appeared to ameliorates pain compared to placebo controls. These results suggest that Chinese herbs can be used in clinical practice for managing chronic pain.

One study included in our meta-analysis showed no effect for relief chronic pain in 39 knee osteoarthritis patients who received orally administrated garlic at 1000 mg/day for 90 days[27]. Although garlic did not show significant efficacy on decreasing pain, it did provide a notable improvement in osteoarthritis stiffness. This result implies that garlic might have other effects on the protection of the knee joint. Srivastava et al.[24] reported that *Curcuma longa* extract had a reduced inflammatory cytokine expression effect in osteoarthritis patients. Morgia et al. indicated that *Curcumin* plus *Calendula* also suppressed chronic pain by rectal suppositories in chronic prostatitis patients[25]. These results indicate that different types and both individual and combinations of Chinese herbs may provide different physiological or pathological effects on chronic pain. Moreover, administration routes also are important factors for chronic pain relief; our meta-analysis found that remission of chronic pain was better for bathing and rectal suppositories than for topical and oral administration. Meanwhile, this study shows that the length of treatment duration might not be a key factor for decreasing chronic pain.

Chinese herbs can be classified by their different meridian organ system entries, and most herbs target more than one meridian entry[28-30]. However, meridian entries are understood as metaphysical concepts[29]. Therefore, the scientific evidence of meridian entry classification remains poorly understood[29]. The liver meridian entry is regarded as corresponding to the nerve–endocrine–immune network, and this theory aligns with the Western medicine discipline of pharmacokinetics[30]. Similarly, our meta-analysis results found that Chinese herbs having a liver meridian entry had good efficacy at attenuating chronic pain. Taken together, we suggest that Chinese herbs could provide a superior effect on the mitigation of chronic pain, particularly those that have a liver meridian entry.

Evidence suggests that chronic pain is driven by neuroinflammation in the nervous system[31]. As we know, chronic pain and morphine tolerance share similar cellular mechanisms[32], which is why chronic pain responds to opioids, but results are unsatisfactory. Previous studies had found that, combined application of Chinese herbal medicine with analgesic drugs maintains the antinociceptive effect of analgesics by down-regulation of microglial activation both in animal and cell line models[33,34] such us *Baicalin* [35,36], *Thunder God Vine*[37,38],

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Ginger[39,40], and *Hericium erinaceus* [41]. These results suggest that if a Chinese herbal medicine which express the ability of regulate immune function then it may have better pain relief efficacy.

This meta-analysis has some limitations: (1) The overall quality of the included studies was not optimal, and some of them had risks of performance and ascertainment bias. (2) No uniform measurement of neuropathic pain exists. The six studies included in the final pooled analysis examined treatment of different chronic pain situations using different methods in terms of intervention, varying different herbs, and inconsistent control therapies. (3) There was a lack of eligible studies examining the efficacy of Chinese herbs for treating chronic pain. (4) The size of the study allowed us to analyze the effectiveness of Chinese herbs, but a much larger study is needed for confirming these results in the future. In summary, our data demonstrates that Chinese herbs significantly attenuate chronic pain. These results indicate that Chinese herbs should be considered a safe, convenient, and independent addition to current chronic pain management options. Although the present meta-analysis indicates positive effects for the use of Chinese herbs for chronic pain management, the administration routes are diverse. In view of the prevalence of Chinese herbs, more RCTs are necessary to fully understand the clinical applications for their use. This meta-analysis suggests that Chinese herbs could be complementary treatment alternatives for patients with chronic pain. Although long-term studies on the effectiveness of Chinese herbs on chronic pain are also available, the number of studies included in this analysis was small. Larger, longer follow-up periods and well-designed studies are needed to be able to draw firm conclusions as to the effectiveness of Chinese herbs in chronic pain relief.

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Conflicts of interest:

The authors declare no conflicts of interest.

Reference

1. Mills SEE, Nicolson KP, Smith BH: Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019; 123: e273-e283.
2. Dale R, Stacey B: Multimodal Treatment of Chronic Pain. Med Clin North Am 2016; 100: 55-64.
3. Breivik H: A major challenge for a generous welfare system: a heavy socio-economic burden of chronic pain conditions in Sweden--and how to meet this challenge. Eur J Pain 2012; 16: 167-169.
4. Cosio D, Lin EH: Effects of a pain education program in Complementary and Alternative Medicine treatment utilization at a VA medical center. Complement Ther Med 2015; 23: 413-422.
5. Lindler BN, Long KE, Taylor NA, Lei W: Use of Herbal Medications for Treatment of Osteoarthritis and Rheumatoid Arthritis. Medicines (Basel) 2020; 7.
6. Ritenbaugh C, Hammerschlag R, Dworkin SF, Aickin MG, Mist SD, Elder CR, Harris RE: Comparative Effectiveness of Traditional Chinese Medicine and Psychosocial Care in the Treatment of Temporomandibular Disorders–Associated Chronic Facial Pain. The Journal of Pain 2012; 13: 1075-1089.
7. Lauche R, Graf N, Cramer H, Al-Abtah J, Dobos G, Saha FJ: Efficacy of Cabbage Leaf Wraps in the Treatment of Symptomatic Osteoarthritis of the Knee: A Randomized Controlled Trial. Clin J Pain 2016; 32: 961-971.
8. Liu P, Liu S, Chen G, Wang P: Understanding channel tropism in traditional Chinese medicine in the context of systems biology. Front Med 2013; 7: 277-279.
9. Higgins JPT, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*, Second edition. ed.; Wiley-Blackwell: Hoboken, NJ, 2020; pp. pages cm.
10. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA,

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Tilling K, White IR, Whiting PF, Higgins JPT: RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

11. Pach D, Brinkhaus B, Roll S, Wegscheider K, Icke K, Willich SN, Witt CM: Efficacy of injections with Disci/Rhus toxicodendron compositum for chronic low back pain--a randomized placebo-controlled trial. PLoS One 2011; 6: e26166.
12. de Vries M, van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, van Goor H: Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. Clin Gastroenterol Hepatol 2017; 15: 1079-1086.e1074.
13. Fan H, Zheng L, Lai Y, Lu W, Yan Z, Xiao Q, Li B, Tang M, Huang D, Wang Y, Li Z, Mei Y, Jiang Z, Liu X, Tang Q, Zuo D, Ye J, Yang Y, Huang H, Tang Z, Xiao J, China Irritable Bowel Syndrome C: Tongxie Formula Reduces Symptoms of Irritable Bowel Syndrome. Clin Gastroenterol Hepatol 2017; 15: 1724-1732.
14. Rabe E, Stucker M, Esperester A, Schafer E, Ottillinger B: Efficacy and tolerability of a red-vine-leaf extract in patients suffering from chronic venous insufficiency--results of a double-blind placebo-controlled study. Eur J Vasc Endovasc Surg 2011; 41: 540-547.
15. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG: Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry 2012; 83: 1125-1132.
16. Romano C, Comito D, Famiani A, Calamara S, Loddo I: Partially hydrolyzed guar gum in pediatric functional abdominal pain. World J Gastroenterol 2013; 19: 235-240.
17. Shakeel S, Usmanghani K, Asif HM: Efficacy and safety of Entoban for the treatment of chronic diarrhea. Pak J Pharm Sci 2016; 29: 2349-2353.
18. Essouiri J, Harzy T, Benaicha N, Errasfa M, Abourazzak FE: Effectiveness of Argan Oil Consumption on Knee Osteoarthritis Symptoms: A Randomized Controlled Clinical Trial. Curr Rheumatol Rev 2017; 13: 231-235.
19. Weiser FA, Fangl M, Mosgoeller W: Supplementation of Caricol®-Gastro reduces chronic gastritis disease associated pain. Neuro Endocrinol Lett 2018; 39: 19-25.
20. Abrams DI, Couey P, Dixit N, Sagi V, Hagar W, Vichinsky E, Kelly ME, Connett JE, Gupta K: Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease: A Randomized Clinical Trial. JAMA Netw Open 2020; 3: e2010874.
21. Raizada MK, Sable DM, Chowdhery A, Chavan MS, Rajpurohit LS: Omega 3: a novel treatment agent in oral submucous fibrosis: a pilot study. J Oral Pathol Med 2017; 46: 439-442.
22. Chrubasik S, Weiser T, Beime B: Effectiveness and safety of topical capsaicin cream in the treatment of chronic soft tissue pain. Phytother Res 2010; 24: 1877-1885.
23. Liu X, Meng Q, Yu D, Zhao X, Zhao T: Novel medical bathing with traditional Chinese herb formula alleviates paraplegia spasticity. Int J Nurs Pract 2014; 20: 227-232.
24. Srivastava S, Saksena AK, Khattri S, Kumar S, Dagur RS: Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. Inflammopharmacology 2016; 24: 377-388.
25. Morgia G, Russo GI, Urzi D, Privitera S, Castelli T, Favilla V, Cimino S: A phase II, randomized, single-blinded, placebo-controlled clinical trial on the efficacy of Curcumina and Calendula suppositories for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome type III. Arch Ital Urol Androl 2017; 89: 110-113.
26. Rich G, Shah A, Koloski N, Funk P, Stracke B, Kohler S, Holtmann G: A randomized placebo-controlled trial on the effects of Menthacarin, a proprietary peppermint- and caraway-oil-preparation, on symptoms and quality of life in patients with functional dyspepsia. Neurogastroenterol Motil 2017; 29.
27. Salimzadeh A, Alipoor E, Dehghani S, Yaseri M, Hosseini M, Feinle-Bisset C, Hosseinzadeh-Attar MJ: The effect of 12-week garlic supplementation on symptom relief in overweight or obese women with knee osteoarthritis. Int J Clin Pract 2018; 72: e13208.
28. Leem J, Jung W, Kim Y, Kim B, Kim K: Exploring the combination and modular characteristics of herbs for alopecia treatment in traditional Chinese

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medicine: an association rule mining and network analysis study. BMC Complement Altern Med 2018; 18: 204.
29. Wang Y, Jafari M, Tang Y, Tang J: Predicting Meridian in Chinese traditional medicine using machine learning approaches. PLoS Comput Biol 2019; 15: e1007249.
30. Liu Z-W, Shu J, Tu J-Y, Zhang C-H, Hong J: Liver in the Chinese and western medicine. Integrative Medicine International 2017; 4: 39-45.
31. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W: Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. Anesthesiology 2018; 129: 343-366.
32. Mayer DJ, Mao J, Holt J, Price DD: Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions. Proc Natl Acad Sci U S A 1999; 96: 7731-7736.
33. Tsai RY, Chou KY, Shen CH, Chien CC, Tsai WY, Huang YN, Tao PL, Lin YS, Wong CS: Resveratrol regulates N-methyl-D-aspartate receptor expression and suppresses neuroinflammation in morphine-tolerant rats. Anesth Analg 2012; 115: 944-952.
34. Yeh CH, Sun LW, Lai CM, Yeh TP, Lin JN, Tsay SL, Chen CC, Chen WP, Chen CM, Tsai RY: Effect of ethanol extracts of Hericium erinaceus mycelium on morphineinduced microglial migration. Mol Med Rep 2019; 20: 5279-5285.
35. Cherng CH, Lee KC, Chien CC, Chou KY, Cheng YC, Hsin ST, Lee SO, Shen CH, Tsai RY, Wong CS: Baicalin ameliorates neuropathic pain by suppressing HDAC1 expression in the spinal cord of spinal nerve ligation rats. J Formos Med Assoc 2014; 113: 513-520.
36. Huang LJ, Jia SS, Sun XH, Li XY, Wang FF, Li W, Jin QS: Baicalin relieves neuropathic pain by regulating alpha2-adrenoceptor levels in rats following spinal nerve injury. Exp Ther Med 2020; 20: 2684-2690.
37. Cameron M, Gagnier JJ, Chrubasik S: Herbal therapy for treating rheumatoid arthritis. Cochrane Database Syst Rev 2011; 10.1002/14651858.CD002948.pub2: CD002948.
38. Yang L, Li Y, Ren J, Zhu C, Fu J, Lin D, Qiu Y: Celastrol attenuates inflammatory and neuropathic pain mediated by cannabinoid receptor type 2. Int J Mol Sci 2014; 15: 13637-13648.
39. Rondanelli M, Fossari F, Vecchio V, Gasparri C, Peroni G, Spadaccini D, Riva A, Petrangolini G, Iannello G, Nichetti M, Infantino V, Perna S: Clinical trials on pain lowering effect of ginger: A narrative review. Phytother Res 2020; 34: 2843-2856.
40. Heidari-Beni M, Moravejolahkami AR, Gorgian P, Askari G, Tarrahi MJ, Bahreini-Esfahani N: Herbal formulation "turmeric extract, black pepper, and ginger" versus Naproxen for chronic knee osteoarthritis: A randomized, double-blind, controlled clinical trial. Phytother Res 2020; 34: 2067-2073.
41. Yi Z, Shao-Long Y, Ai-Hong W, Zhi-Chun S, Ya-Fen Z, Ye-Ting X, Yu-Ling H: Protective Effect of Ethanol Extracts of Hericium erinaceus on Alloxan-Induced Diabetic Neuropathic Pain in Rats. Evid Based Complement Alternat Med 2015; 2015: 595480