Pharmacopuncture with Herbal Medicine Extracts Effect in Women with Cervical Spondylosis: A Meta-analysis

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Abstract **Background:** A meta-analysis was performed to evaluate the efficacy and safety of pharmacopuncture in women with cervical spondylosis. **Methods:** A systematic literature search from up to July 2021 was performed and 18 studies included 1566 women with cervical spondylosis at the start of the study; 813 of them were using pharmacopuncture, 219 were control, and 582 were using other treatments. They were reporting relationships between the efficacy and safety of pharmacopuncture in women with cervical spondylosis. The mean difference (MD) with its 95% confidence intervals (CIs) was calculated to assess the efficacy and safety of pharmacopuncture in women with cervical spondylosis using the continuous method with a random or fixed-effect model. **Results:** Pharmacopuncture in women with cervical spondylosis was significantly related to lower Visual analog scale (MD, -1.80; 95% CI, -2.33- -1.27, p<0.001), and no significant difference was found related to the McGill pain questionnaire (MD, -2.11; 95% CI, -4.89- -0.68, p=0.14) compared to control. Pharmacopuncture combined with other treatment in women with cervical spondylosis was significantly related to lower Visual analogue scale (MD, -1.79; 95% CI, -2.24- -1.34, p<0.001), lower Visual analogue scale after 3 months follow up (MD, -1.88; 95% CI, -3.36- -0.41, p=0.01), and higher SF-36 questionnaire (MD, 18.31; 95% CI, 13.33-23.29, p<0.001) compared to other treatment. **Conclusions:** Pharmacopuncture in women with cervical spondylosis was significantly related to the lower Visual analog scale, and no significant difference was found related to the McGill pain questionnaire compared to control. Pharmacopuncture combined with other treatments in women with cervical spondylosis was significantly related to lower Visual analog scale, lower Visual analog scale after 3 months follow up, and higher SF-36 questionnaire compared to other treatments.

Keywords: pharmacopuncture, cervical spondylosis, Visual analog scale, McGill pain questionnaire, 3 months follow up, SF-36 questionnaire

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1. Background

Neck pain is a common musculoskeletal disorder that influences everyday life, often causing disability and increased health care costs. The 2010 Global Burden of Disease stated that neck pain is the fourth major reason to live with a disability, after back pain, major depressive disorder, and other musculoskeletal disorders. [1] It was stated that almost two-thirds of the overall population experience neck pain in their lives in Canada. [2] However, another Korean study has shown that a lifetime neck pain incidence was 20.8%. [3] A previous meta-analysis on neck pain stated that the normal lifetime incidence of neck pain in adult populations was almost 50%. [4] Women experience neck pain more often than men, [3,4] and neck pain has been related to smoking, obesity, and the female gender. [3] Acute neck pain is defined as pain within 6 weeks of onset and typically resolves within 2 months. Though, almost half of all the acute cases experience pain recurrence 1 year later or progress to chronic pain. [5,6] Of the diverse factors that add to the progress of chronic pain are mechanical loading, stress, and degenerative changes. Cervical spondylosis symptoms are defined as neck stiffness, restricted range of motion, and cervical pain that tends to be intensified by movement, and are supplemented by degenerative changes of the intervertebral disc with the osteophyte formation. [7]

Injections and medication are considered the first-line management for neck pain comprising cervical spondylosis. Non-steroidal anti-inflammatory drugs are often effective against spinal pain. [8] However, they often cause adverse events e.g. gastritis, myocardial infarction, gastric ulcers,

and internal bleeding. [9,10] While trigger-point and epidural steroid injections are the most common forms of injection used, [11] Scott et al. showed that trigger-point injection usage in chronic musculoskeletal complaints lacks strong evidence. [12] Epidural steroid injections do not produce favorable results when combined with chronic opioid usage, [13] and epidural steroid injections usage has been related to several difficulties e.g. epidural hemorrhage, spinal or neuronal injury, infections, vascular perforation, and arachnoid perforation. [14] Recurrent or chronic symptoms of neck pain might progress as a result of failed first-line management or its restrictions, and subject interest in complementary and alternative medicine care. In the USA, interest in the use of complementary and alternative medicine for neck, and back pain is progressively growing. [15] The latest meta-analysis has shown that acupuncture management for neck pain is safe and effective since it has few side effects. 16 Another recent study has shown that herbal medicine is effective in cervical spondylosis. [17] Pharmacopuncture is a quite new category of acupuncture management used in East Asian medicine. [18] Pharmacopuncture treatment injects herbal medicine extracts at exact acupuncture or reflex points based on subject structure and disease pathology. Pharmacopuncture and acupuncture are both often used in Korean medicine clinics and hospitals for more effective care of musculoskeletal complaints. [19] Though a small number of reports suggest the use of pharmacopuncture for intractable complaints, [20] however, insufficient data support these claims. This meta-analysis aimed to evaluate the efficacy and safety of pharmacopuncture in women with cervical spondylosis.

2. Methods

The study completed here followed the meta-analysis of studies in the epidemiology statement, [21] following an established protocol.

2.1. Study Selection

Studies comprised were that stated statistical measures of relationship (odds ratio [OR], mean difference [MD], frequency rate ratio, or relative risk, with 95% confidence intervals [CIs]) measuring the efficacy and safety of pharmacopuncture in women with cervical spondylosis.

Only human studies in any language were selected. Inclusion was not limited by study type or size. Studies excluded were commentary and review articles and articles that did not provide a degree of association. Figure 1 shows the whole study process.

The articles were included in our meta-analysis when the next inclusion criteria were met:

1. The study was a prospective study or retrospective.

2. The target population is women with cervical spondylosis

3. The intervention program was the pharmacopuncture

4. The study comprised comparisons between the efficacy and safety of pharmacopuncture in women with cervical spondylosis

The exclusion criteria were:

1. Studies that did not compare pharmacopuncture to other treatments

2. Studies with diseases other than cervical spondylosis

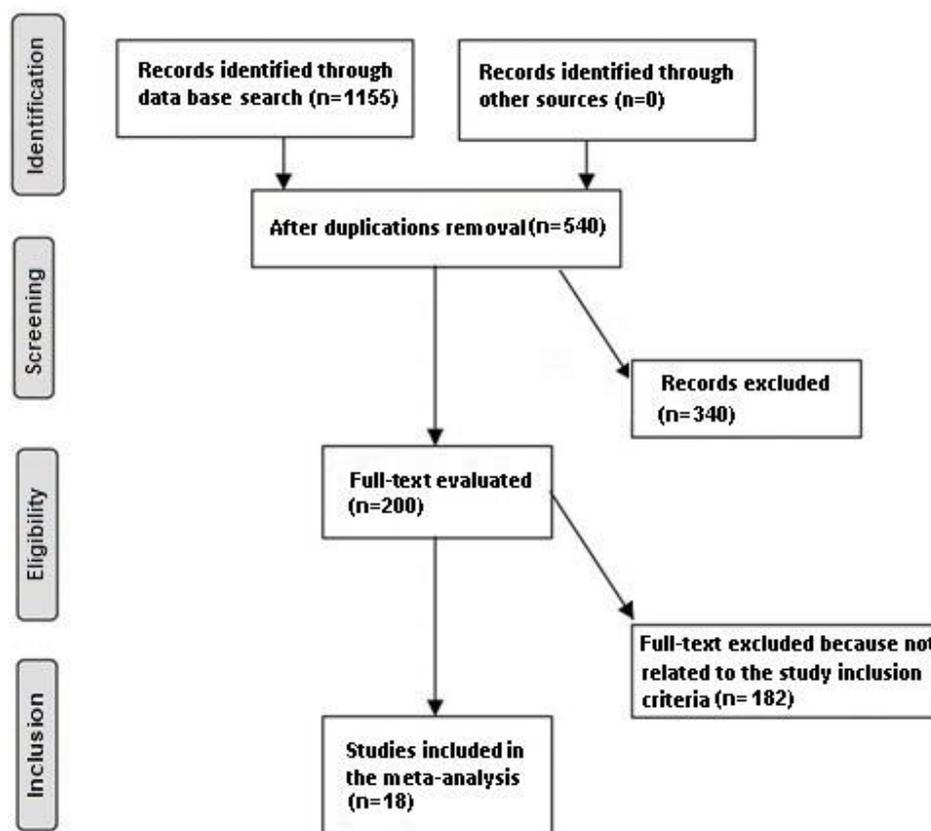3. Studies did not concentrate on the effect of comparative results.

Figure 1. Diagram of the study process

2.2. Identification

A search protocol strategy was organized according to the PICOS principle, [22] as follow: P (population): women with cervical spondylosis; I (intervention/exposure): pharmacopuncture; C (comparison): the efficacy and safety of pharmacopuncture in women with cervical spondylosis compared to other treatments; O (outcome): Visual analog scale, McGill pain questionnaire, and SF-36 questionnaire; and S (study design): no restriction. [23] First, a systematic search was conducted of China National Knowledge Infrastructure, Korean language-based databases, China National Knowledge Infrastructure OVID, Embase, Cochrane Library, PubMed, and Google scholar, till July 2021, using a blend of keywords and similar words for pharmacopuncture, cervical spondylosis, Visual analog scale, McGill pain questionnaire, 3 months follow up, and SF-36 questionnaire as shown in Table 1. Selected studies were collected in an EndNote file, duplicates were omitted, and the title and abstracts were reviewed to remove studies that did not report the association between the efficacy and safety of pharmacopuncture in women with cervical spondylosis based on the previously mentioned exclusion and inclusion criteria. The remaining articles were revised for associated information.

Table 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "pharmacopuncture"[MeSH Terms] OR "cervical spondylosis"[All Fields] OR "Visual analogue scale"[All Fields]
	#2 "McGill pain questionnaire"[MeSH Terms] OR "pharmacopuncture"[All Fields] OR "3 months follow up"[All Fields] OR "SF-36 questionnaire"[All Fields]
	#3 #1 AND #2
Embase	'pharmacopuncture'/exp OR 'cervical spondylosis'/exp OR 'Visual analogue scale'/exp
	#2 'McGill pain questionnaire'/exp OR 'ICBG'/exp OR '3 months follow up' OR 'SF-36 questionnaire'
	#3 #1 AND #2
Cochrane library	#1 (pharmacopuncture):ti,ab,kw OR (cervical spondylosis):ti,ab,kw OR (Visual analogue scale):ti,ab,kw (Word variations have been searched)
	#2 (McGill pain questionnaire):ti,ab,kw OR (3 months follow up):ti,ab,kw OR (SF-36 questionnaire):ti,ab,kw (Word variations have been searched)
	#3 #1 AND #2

2.3. Screening

Data were abbreviated based on the following; study associated and woman associated features onto a homogeneous form. the primary author last name, study period, publication year, country, the studies region, and design of the study; type of the population, the total number and women number, demographic data and clinical and treatment features; the evaluation period associated with measurement, quantitative method and qualitative method of assessment, source of information, and outcomes' assessment; and statistical analysis MD or relative risk, with 95% CI of relationship among the efficacy and safety of pharmacopuncture in women with cervical spondylosis. [24] If a study fit for inclusion based upon the above-mentioned principles, data were extracted individually by two authors. In case of discrepancy, the corresponding author gave a final choice. When there were diverse data from a study, the data were extracted separately. The bias risk in the studies; each study was assessed using two authors who individually evaluated the methodological quality of the selected studies. We used the "risk of bias tool" from the RoB 2: A revised Cochrane risk-of-bias tool for randomized trials to evaluate methodological quality. [25] In terms of the evaluation criteria, each study was valued and allocated to one of the next three risks of bias: low, if all quality criteria were met; unclear or moderate, if one or more of the quality criteria were partly met or unclear; or high, if one or more of the criteria were not met, or not included. Any discrepancies were addressed by a reassessment of the original article.

2.4. Eligibility

The main result concentrated on measuring the efficacy and safety of pharmacopuncture in women with cervical spondylosis. Evaluation of the measuring the efficacy and safety of pharmacopuncture in women with cervical spondylosis was extracted forming a summary.

2.5. Inclusion

Sensitivity analyses were restricted only to studies showing a relationship between the efficacy and safety of pharmacopuncture in women with cervical spondylosis. For subcategory and sensitivity analysis, the effect of pharmacopuncture compared to control and pharmacopuncture combined with other treatment compared to other treatment was used.

2.6. Statistical Analysis

We determine the Mean difference (MD) and 95% confidence interval (CI) using the continuous technique with a fixed-effect or random-effect model. We determined the I^2 index and the I^2 index was alternated between 0% and 100%. When the I^2 index was about 0%, 25%, 50%, and 75% that identifies no, low, moderate, and high heterogeneity, respectively. [22] We used the random-effect if the I^2 was > 50%; we used the fixed-effect if it was < 50%. We used stratifying the original evaluation per outcome categories as described before to complete the subgroup analysis. A p-value for differences between subcategories of <0.05 was considered statistically significant. Publication bias was evaluated quantitatively using the Egger regression test (publication bias is existing if p≥0.05), and qualitatively, by visual examination of funnel plots of the logarithm of odds ratios against their standard errors. [24] The whole p-values were 2 tailed. Reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to do all calculations and graphs.

3. Results

A total of 1155 unique studies were selected, of which 18 studies up to July 2021 satisfied the inclusion criteria and were comprised in the study. [26-43]

The 18 studies included 1566 women with cervical spondylosis at the start of the study; 813 of them were using pharmacopuncture, 219 were control, and 582 were using other treatments. All studies evaluated the efficacy and safety of pharmacopuncture in women with cervical spondylosis.

Study size ranged from 55 to 156 women with cervical spondylosis at the start of the study. All the studies were performed in China and Korea. The details of the 18 studies are presented in Table 2. 6 studies reported a comparison between pharmacopuncture and control, 11 studies comparison pharmacopuncture combined with other treatment compared to other treatment, and one study reported both comparisons.

Pharmacopuncture in women with cervical spondylosis was significantly related to lower Visual analogue scale (MD, -1.80; 95% CI, -2.33- -1.27, p<0.001) with high heterogeneity (I^2 = 86%), and no significant difference was found related to McGill pain questionnaire (MD, -2.11; 95% CI, -4.89- -0.68, p=0.14) with high heterogeneity (I^2 = 94%) compared to control as shown in Figure 2, Figure 3.

Table 2. Characteristics of the selected studies for the meta-analysis

| Study	Total	Pharmacopuncture	Control	Other treatment
Y. Liu, 2008 [26]	60	30	30	
Y. Liu, 2009 [27]	55	28	27	
X. Zhang, 2011 [28]	108	78	30	48
L. Li, 2012 [29]	96	48		48
S.-J. Zeng, 2012 [30]	80	40	40	
H. Zhao, 2013 [31]	140	70		70
Gao, 2013 [32]	82	41		41
L.-P. Li, 2014 [33]	64	32		32
H. Wang, 2014 [34]	62	31	31	
Y. Xie, 2014 [35]	105	54		51
W. Zhang, 2015 [36]	156	78		78
C. Qui, 2015 [37]	105	56		49
S.-R. Wei, 2016 [38]	60	30		30
X.-J. Wang, 2016 [39]	60	30	30	
X. Wen, 2016 [40]	90	45		45
J. Yang, 2016 [41]	78	39		39
Zhang, 2017 [42]	102	51		51
Zhang, 2019 [43]	63	32	31	
Sum	**1566**	**813**	**219**	**582**
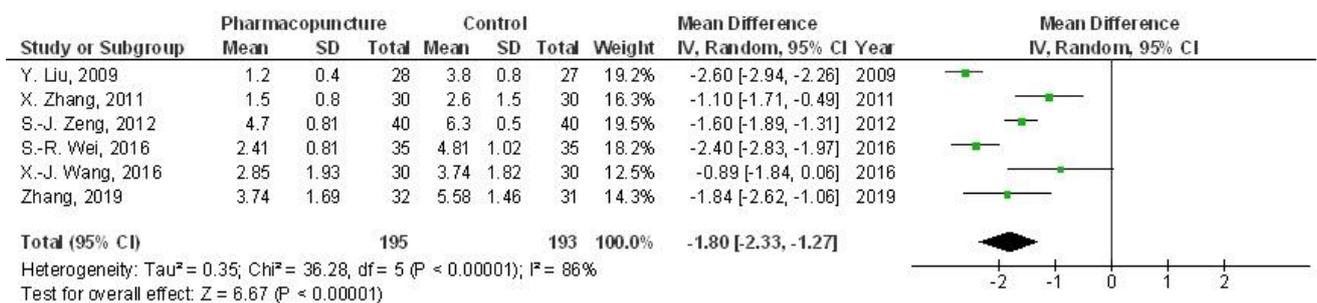
Figure 2. Forest plot of the outcome of pharmacopuncture compared to control on Visual analog scale in women with cervical spondylosis
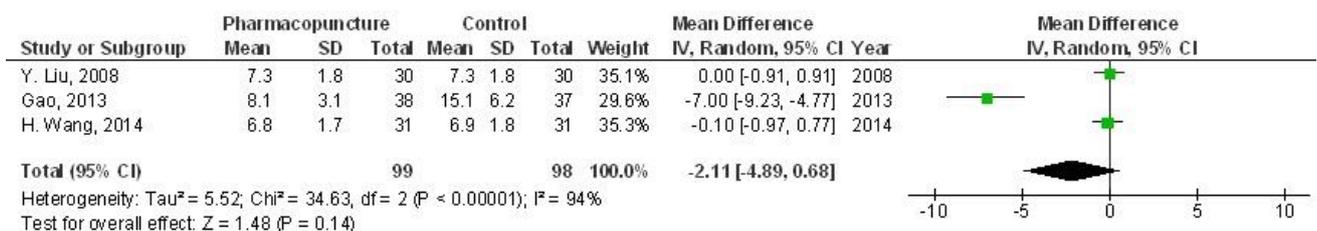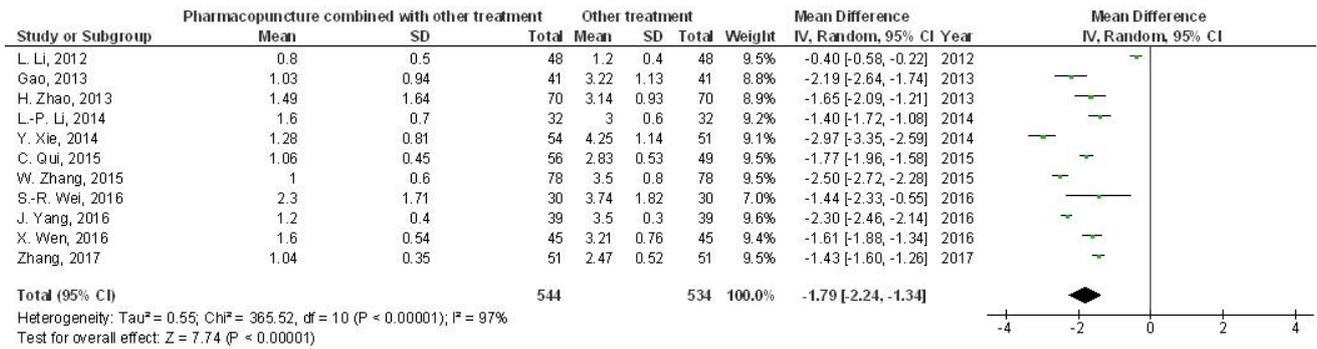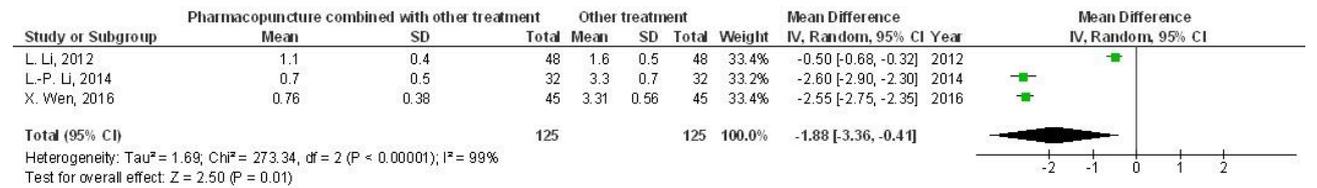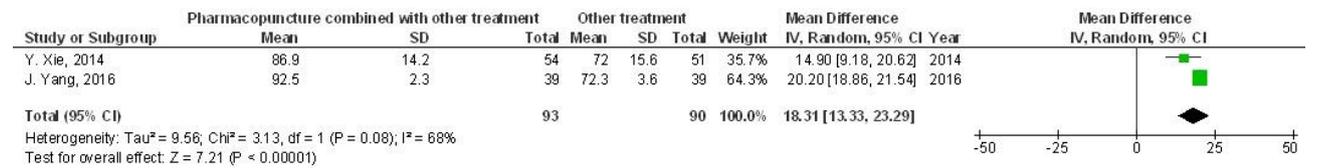

Figure 3. Forest plot of the outcome of pharmacopuncture compared to control on McGill pain questionnaire with cervical spondylosis

Figure 4. Forest plot of the outcome of pharmacopuncture combined with other treatment compared to other treatment on Visual analog scale in women with cervical spondylosis

Figure 5. Forest plot of the outcome of pharmacopuncture combined with other treatment compared to other treatment on Visual analog scale after 3 months follow up in women with cervical spondylosis

Figure 6. Forest plot of the outcome of pharmacopuncture combined with other treatment compared to other treatment on SF-36 questionnaire in women with cervical spondylosis

Pharmacopuncture combined with other treatment in women with cervical spondylosis was significantly related to lower Visual analogue scale (MD, -1.79; 95% CI, -2.24- -1.34, p<0.001) with high heterogeneity (I^2 = 97%), lower Visual analogue scale after 3 months follow up (MD, -1.88; 95% CI, -3.36- -0.41, p=0.01) with high heterogeneity (I^2 = 99%), and higher SF-36 questionnaire (MD, 18.31; 95% CI, 13.33-23.29, p<0.001) with moderate heterogeneity (I^2 = 68%) compared to other treatment as shown in Figure 4 – Figure 6.

Selected studies stratified analysis that adjusted for age, and ethnicity was not performed since no studies reported or adjusted for these factors. Based on the visual examination of the funnel plot as well as on quantitative assessment by the Egger regression test, there was no indication of publication bias (p = 0.88). Though, most of the comprised studies were evaluated to be of a low methodological quality. All selected studies did not have selective reporting bias, and no articles had incomplete result data and selective reporting.

4. Discussion

This meta-analysis study based on 18 studies included 1566 women with cervical spondylosis at the start of the study; 813 of them were using pharmacopuncture, 219 were control, and 582 were using other treatments [26-43] Pharmacopuncture in women with cervical spondylosis was significantly related to lower Visual analog scale, and no significant difference was found related to McGill pain questionnaire compared to control. Pharmacopuncture combined with other treatments in women with cervical spondylosis was significantly related to lower Visual analog scale, lower Visual analog scale after 3 months follow up, and higher SF-36 questionnaire compared to other treatments. [26-43]

However, the analysis of results should be done with caution due to the low number of studies in the present meta-analysis, most of the selected studies were performed in two countries (China, and Korea), and many of the selected studies were of low sample size (12 of of 18 studies were ≤100 women); proposing the requirement for additional studies evaluating the efficacy and safety of pharmacopuncture in women with cervical spondylosis to validate these findings. The need for more studies is very obvious since many comparisons were based on 2 or 3 studies, showing the need for further research possibly to significantly affect confidence in the effect assessment.

The current meta-analysis assessed randomized clinical trials examining the influence of pharmacopuncture management of cervical spondylosis. Most randomized clinical trials implemented active controls e.g. acupuncture and Tuina management methods rather than the only placebo e.g. saline. The present effect of pharmacopuncture might be due to the phytochemical influence of herbal extracts of pharmacopuncture when added to traditional acupuncture. Moreover, management plans and study duration require to be taken into consideration in the study analysis and are of intensified interest in cervical spondylosis as its symptoms that appear chronically. Many randomized clinical trials

assessed results after 3 to 5 weeks of management, while others assessed results after only about 2 weeks' management. The study by Liu [26] detected results after a single management session, while the study by Wang [34] was performed over three weeks. The management influences after 12 sessions were more significantly effective than a single session as shown by Liu [26] and Wang. [34] Hence, randomized clinical trials of a longer period of management plans are necessary to evaluate the efficacy of pharmacopuncture in cervical spondylosis. Pharmacopuncture is only management was frequently studied for a management period of two weeks or less but mostly at high rate of recurrence, while studies of add-on management design were mostly performed for 3 to 5 weeks' management, except for the studies by Liu [26] and Wang. [39] So, it is recommended that randomized clinical trials are required to be planned with a management period of three weeks or more to validate the management influence of pharmacopuncture for cervical spondylosis. The safety of pharmacopuncture can be determined by evaluating the rarely reported adverse events of pharmacopuncture. However, the value of evidence for the outcomes of the adverse event was shown to be low or very low.

The included randomized clinical trials have shown that pharmacopuncture improves pain over traditional acupuncture, and the fundamental mechanism is expected to include supplementary mechanisms other than physical stimulation. A mixture of physical and chemical stimuli by acupoint needling with herbal medication injected is assumed to result in its therapeutic effects. [44] The pharmacopuncture types studied in the present meta-analysis involved compound Angelica sinesis and compound Salvia miltiorrhiza. Salvia miltiorrhiza contains salcianolic acid B which exhibits anti-hyperalgesic activity in neuropathic pain. [45] Angelicae Sines Radix has been used in China, Japan, and Korea as an anti-inflammatory, anti-fibrotic, and neuro-protective. [46] Ligustilide, the main component of the herb, was found to exert anti-inflammatory effects, which could be related to its analgesic properties. [47] The randomized clinical trials on the pharmacopuncture were performed based on their previously described pharmacological mode of action and effects. Pharmacopuncture was shown to improve pain over acupuncture, and also reduced pain as add-on management to acupuncture or other care techniques; the management effect was sustained over the follow-up period, and the quality of life was also improved by pharmacopuncture management.

This meta-analysis reported the association between pharmacopuncture use and effects in women with cervical spondylosis. Though, additional studies are required to confirm these possible relations. Moreover, additional studies are required to supply a clinically meaningful difference of the outcomes in women with cervical spondylosis. These studies must include larger homogeneous samples. This was recommended similarly in an earlier similar meta-analysis study which reported a comparable effect of pharmacopuncture and control in women with cervical spondylosis. [9]

Well-conducted studies are furthermore needed to assess these factors and the mixture of different ages, and ethnicity; since our meta-analysis study could not answer whether they are associated with the results. Also, standardization of pharmacopuncture type, acupoints, management duration, and follow-up periods are required qualities of upcoming studies. Additionally, pharmacopuncture safety could not be adequately evaluated because of the lack of studies showing the adverse events. Most of the selected randomized clinical trials reported that no severe adverse events were related to pharmacopuncture. One retrospective study showed that adverse events from pharmacopuncture rarely happen. [48] Additional prospective studies are needed to clarify the pharmacopuncture safety for cervical spondylosis.

In summary, the data recommend that pharmacopuncture in women with cervical spondylosis was significantly related to the lower Visual analog scale, and no significant difference was found related to the McGill pain questionnaire compared to control. Pharmacopuncture combined with other treatments in women with cervical spondylosis was significantly related to the lower Visual analog scale, lower Visual analog scale after 3 months follow up, and higher SF-36 questionnaire compared to other treatments. Furthers studies are needed to confirm these findings.

5. Limitations

There may be selection bias in this study since several selected studies were excluded from the meta-analysis. However, the excluded studies did not satisfy the inclusion criteria of our meta-analysis. Similarly, whether the outcomes are related to age and ethnicity or not could not be answered. The study designed to evaluate the efficacy and safety of pharmacopuncture in women with cervical spondylosis was based on data from earlier studies, which may result in bias persuaded by incomplete details. The meta-analysis was based on a small number of studies (18 studies); 12 studies were small, ≤ 100. Variables including age, ethnicity, and nutritional status of women were also the possible bias-inducing factors. Some unpublished articles and missing data may cause a bias in the pooled result. Women were using different dosages, management schedules, and health care systems. The data could also be affected by other management(s), causing variation in effect size.

6. Conclusions

Pharmacopuncture in women with cervical spondylosis was significantly related to the lower Visual analog scale, and no significant difference was found related to the McGill pain questionnaire compared to control. Pharmacopuncture combined with other treatments in women with cervical spondylosis was significantly related to the lower Visual analog scale, lower Visual analog scale after 3 months follow up, and higher SF-36 questionnaire compared to other treatments. However, the analysis of results should be done with caution due to the low number of studies in the present meta-analysis, most of the selected studies were performed in two countries, and many of the selected studies were of low sample size; proposing the requirement for additional

studies evaluating the efficacy and safety of pharmacopuncture in women with cervical spondylosis to validate these findings.

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