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Literature Review of Domestic Randomized Controlled Trials for Hominis Placenta Pharmacopuncture

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This study was conducted to analyze research trends, quality, and bias of pharmacopuncture studies, etc., on domestic randomized controlled trials (RCTs) using hominis placenta pharmacopuncture (HPP). A total of 13 domestic RCTs were selected by searching two domestic online databases (Research Information Sharing Service and Oriental Medicine Advanced Searching Integrated System). The publication of domestic RCTs using HPP began in 2000, and most studies targeted peripheral facial paralysis and gynecological diseases. Most studies have shown the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist reporting rate of > 50.0%; however, four subitems, including "depth of insertion," showed a reporting rate < 50.0%. Some studies have shown significant improvement in the HPP group; however, the sample size was diverse, the observation period was short, the effect of stimulation of the same acupoint between the two groups could not be ruled out, and the overall risk of bias was mostly "some concern." In addition, further development of STRICTA that reflects the characteristics of pharmacopuncture therapy is necessary.

Keywords: Pharmacopuncture; Placenta; Randomized controlled trial; Review

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INTRODUCTION

Pharmacopuncture therapy is a method of administering pharmacopuncture solution prepared by various methods to acupuncture points related to diseases, positive reaction points (tender points and Ashi-point) obtained through body surface stimulation and blood vessels using a syringe for pharmacopuncture injection. It is a new acupuncture method of treating diseases using the efficacy of acupuncture and medicine, adjusting body functions, and improving pathological conditions. It was the result of the emergence of new treatment methods over time [1], and this treatment method involves both physical stimulation in acupuncture and chemical stimulation in the pharmacological action of a pharmacopuncture solution. This combination strengthens and prolongs the treatment effect on acupuncture points [2].

Hominis placenta is derived from newborn placenta without blood vessels, washed, and dried. It contains several endocrine hormones and is effective in treating menstrual irregularities, chronic debilitating diseases, nervous breakdown, and infertility [3]. Pharmacopuncture preparations made from these ingredients are injected subcutaneously or intramuscularly and are used to treat infertility, menopausal disorders, physical weakness, nervous breakdown, and prostate hypertrophy [4].

In the Korean medicine community, interest in and clinical trials as evidence-based medicine are gradually increasing, clinical trials on acupuncture have recently become active in Korea, and protocols are being established [5]. Experimental, observational, and descriptive studies have certain significance; however, as evidence-based medicine becomes the center of clinical care, clinical research has become important, and among them, randomized controlled clinical trial (RCT) is considered the best to verify the effectiveness of medical technology [6].

Many studies reviewing RCTs on acupuncture have been published; however, the number of RCT review studies targeting pharmacopuncture, a new type of acupuncture, is relatively small [6,7], and no review study on domestic RCTs of hominis placenta pharmacopuncture (HPP) has been published. Thus, the present study was conducted to serve as a basis for future research.

MATERIALS AND METHODS

1. Search strategy

RCTs using HPP were the subject of the search using domestic databases Research Information Sharing Service and Oriental Medicine Advanced Searching Integrated System. The search terms were set to “Hominis placenta” (in English, Korean, and Chinese), “hominis placenta pharmacopuncture” (in Korean), and “Pharmacopuncture.” The titles and abstracts of the retrieved studies were checked to first exclude duplicate studies. Then non-RCT studies such as experimental and case studies were excluded, resulting in a total of 13 RCTs [8-20] selected as research subject (Table 1, Fig. 1).

2. Assessing bias and quality of the reporting of pharmacopuncture

The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) reporting guidelines were created to improve the completeness and transparency of intervention reporting in comparative acupuncture clinical trials. Since its first publication in 2001, revisions have been proposed through various surveys, resulting in the 2010 STRICTA checklist, which consists of six items and 17 subitems, and is designed to help improve intervention reporting in acupuncture clinical trials [21]. Because pharmacopuncture is a new acupuncture method [1], the quality of reporting was assessed using the 2010 STRICTA checklist. However, unlike acupuncture, pharmacopuncture uses a syringe for pharmacopuncture injection [1] and has the characteristics of being performed by extracting the syringe immediately rather than needle retention, and this was partially reflected in the evaluation.

The risk of bias (RoB) of the 13 RCTs was assessed using the revised Cochrane RoB tool for randomized trials (RoB 2) [22]. The RoB tool assesses biases occurring at different stages of selected trials based on empirical evidence and theoretical considerations [23] and in response to signal questions for a total of five areas, three levels of RoB (low risk, some concerns, and high risk) were specified according to the mapping algorithm [24].

RESULTS

1. Publication year

The publication of an RCT targeting HPP began in 2000 [14], and the largest number of RCTs published was four in 2005 [12,13,15,16], two in 2010 [9,10], and one each in 2001 [8], 2006 [17], 2008 [11], 2009 [18], 2021 [19], and 2022 [20] (Table 1).

Table 1. List and summary of selected randomized controlled trials

Author (y)	Journal	Target disease*	Study participant	
			N (C/I)†	n (C/I)
Sin et al. (2001) [8]	*Journal of Pharmacopuncture*	Peripheral facial palsy	41 (30/11)	Discharged during recovery (no data)
Park et al. (2010) [9]	*Journal of Korean Acupuncture & Moxibustion Society*	Peripheral facial paralysis	36 (18/18)	-
Kim et al. (2010) [10]	*Journal of Oriental Obstetrics & Gynecology*	Postpartum women's heat feeling, sweats, and thirst	25 (12/13)	7 (no data)
Kim et al. (2008) [11]	*Journal of Pharmacopuncture*	Dysmenorrhea	49 (24/25)	-
Yoo et al. (2005) [12]	*Journal of Pharmacopuncture*	Menstrual cramps	8 (4/4)	-
Chang et al. (2005) [13]	*Journal of Korean Acupuncture & Moxibustion Society*	Dysmenorrhea	14 (no data)	-
Yun et al. (2000) [14]	*Journal of the Korean Institute of Herbal Acupuncture*	Bell's palsy	16 (8/8)	-
Youn et al. (2005) [15]	*Journal of Pharmacopuncture*	Sleep pattern disturbance	48 (23/25)	10 (6/4)
Lee et al. (2005) [16]	*Journal of Pharmacopuncture*	Bell's palsy	44 (21/23)	9 (no data)
Park et al. (2006) [17]	*Journal of Korean Acupuncture & Moxibustion Society*	Osteoarthritis of the knee joint	60 (30/30)	-
Noh et al. (2009) [18]	*Journal of Pharmacopuncture*	Leg spasticity in patients with stroke	20 (9/11)	3 (no data)
Kim et al. (2021) [19]	*Journal of Oriental Neuropsychiatry*	Mild cognitive impairment	29 (14/15)	1 (1/0)
Choi et al. (2022) [20]	*Integrative Medicine Research*	Hot flashes in peri- and post-menopausal women	103 (35/68)	25 (8/17)

C, control group; I, intervention group; n, number of dropouts during study.
*In the format mentioned in the paper. †Final number of study participants excluding dropouts.

2. Academic journal

A total of 13 RCTs were published, 7 in the Journal of Pharmacopuncture (formerly, *Journal of the Korean Institute of Herbal Acupuncture*), 3 in the *Journal of Korean Acupuncture & Moxibustion Society*, 1 in the *Journal of Oriental Obstetrics & Gynecology*, 1 in the *Journal of Oriental Neuropsychiatry*, and 1 in *Integrative Medicine Research* (Table 1).

3. Target disease

The diseases targeted in HPP RCTs were peripheral facial paralysis in 4 RCTs [8,9,14,16], dysmenorrhea in 3 [11-13], and postpartum disease [10], sleep pattern disturbance [15], degenerative knee arthritis [17], leg spasticity in patients with stroke [18], mild cognitive impairment [19], and perimenopausal hot flashes [20] in one RCT each (Table 1).

4. Number of study participants

The largest RCT had 128 study participants [20], and the smallest had 8 [12]. Moreover, 3 RCTs [15-17] targeted 51–60 participants and 2 RCTs each enrolled 11–20 [13,14], 21–30 [18,19], 31–40 [9,10], and 41–50 [8,11] (Table 1).

5. Control and intervention group settings

In the control group, acupuncture had the largest number of RCTs conducted, with three RCTs [8,12,15], followed by saline injection [11,19] and saline injection and physiotherapy [13,20], with two RCTs each. Moreover, acupuncture, sweet bee venom, herbal medicine, and Western medicine [9]; acupuncture, saline injection, and herbal medicine [10]; acupuncture, herbal medicine, and physiotherapy [14]; acupuncture, saline injection, physiotherapy, herbal medicine, and Western medicine [16]; acupuncture and physiotherapy [17]; and acupuncture and saline injection [18] had one RCT each (Table 2).

Among the five RCTs [8,11,12,15,19] in which the control group consisted of only one treatment method, two RCTs [11,19] had the control group receiving saline and the intervention group received HPP. In addition, in three RCTs [8,12,15], the control group received acupuncture, whereas the intervention groups received acupuncture and pharmacopuncture [8], acupuncture and HPP [12], and HPP [15] (Table 2).

Among RCTs with two or more treatments in the control group [9,10,13,14,16-18,20], saline solution [10,13,16, 18,20] or sweet bee venom [9] were administered to the control group as a placebo pharmacopuncture. In the in-

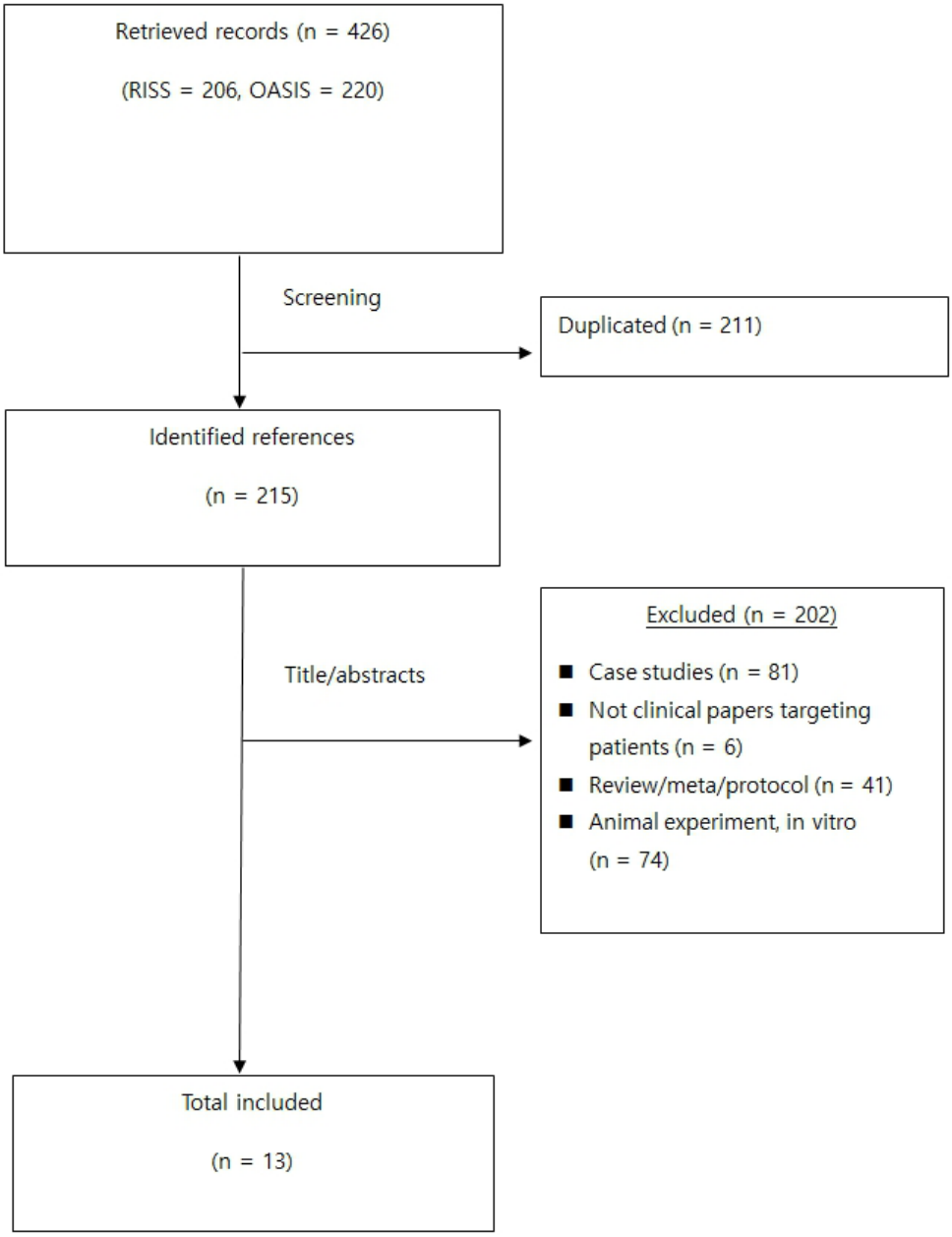

Fig. 1. Flow chart. RISS, Research Information Sharing Service; OASIS, Oriental Medicine Advanced Searching Integrated System.

tervention group, HPP was added to the control treatment [14], or acupuncture was performed in the control group instead of HPP in the intervention group [17] (Table 2).

6. Treatment method

Based on the STRICTA checklist, reports and treatment methods of HPP were analyzed.

1) Acupuncture rationale

(1) Style of acupuncture

Among the 13 RCTs, pharmacopuncture [8,10,12,14-17,19,20] or HPP [9,10,12,14-17,19,20] was described in a total of 10 RCTs [8-10,12,14-17,19,20], and 3 RCTs [11,13,18] described hominis placenta but did not specify the pharmacopuncture (Table 3).

Table 2. Summary of treatment content, evaluation scales, and treatment results for both groups

Author (IRB)	Intervention group treatment	Control group treatment	Evaluation scale	Significance of the intervention group compared with the control group (I/C)	Adverse event (I/C)
Sin et al. [8]	1. Acu 2. PA (include HPP)	1. Acu	1. Assessment of facial muscle paralysis 2. Period until movement of BL2 appears	1. NS 2. NR	NR
Park et al. [9]	1. Acu 2. HPP 3. HM + WM	1. Acu 2. SBV 3. HM + WM	1. Yanagihara's unweighted grading system 2. Comparison of improvement index	1. NS 2. NS	NR
Kim et al. (IRB+) [10]	1. HPP 2. HM 3. Acu	1. N/S (inj.) 2. HM 3. Acu	1. 7-zone-diagnostic system 2. HRV 3. VAS 4. CBC	1. NS 2. Ln (LF): $p < 0.01$ 3. NS 4. NS	None
Kim et al. [11]	1. HPP	1. N/S (inj.)	1. MMP 2. MSSL	1. NS 2. NS	NR
Yoo et al. [12]	1. Acu 2. HPP	1. Acu	1. VAS	1. $p = 0.057$	NR
Chang et al. [13]	1. HPP 2. Physio	1. N/S (inj.) 2. Physio	1. VAS 2. D.I.T.I.	1. $p < 0.05$ 2-1. Difference rate of the average abdominal temperature value: $p < 0.05$ 2-2. Rate of change in the left and right abdominal temperature difference: $p < 0.05$ 2-3. Changes in abdominal temperature imbalance: (decrease/no major changes)	NR
Yun et al. [14]	1. Acu 2. HPP 3. HM 4. Physio	1. Acu 2. HM 3. Physio	1. Assessment of paralytic degree	1. NR	NR
Youn et al. [15]	1. HPP	1. Acu	1. Sleep pattern disturbance score (based on Korean sleep scale A) 2. Treatment satisfaction	1. t = 7.00, $p = 0.00$ 2. (80%/61%)	NR
Lee et al. [16]	1. HPP 2. Acu 3. HM 4. Physio 5. WM	1. N/S (inj.) 2. Acu 3. HM 4. Physio 5. WM	1. Yanagihara's unweighted grading system	1-1. Baseline–after 3 wk: NS 1-2. After 4 wk: $p = 0.047$ 1-3. After 5 wk: $p = 0.032$	NR
Park et al. [17]	1. HPP 2. Physio	1. Acu 2. Physio	1. Ahlaback classification 2. Lysholm score 3. Nine-point scale by Baumgartner	1. NS 2. NS 3. (63.3%/50.0%)	NR
Noh et al. (IRB-) [18]	1. HPP 2. Acu	1. N/S (inj.) 2. Acu	1. MAS 2. H/M ratio 3. BBS 4. TUG	1. NS 2. NS 3. 2–3 wk: $p = 0.01$ 4. Baseline–3 wk: $p = 0.04$	NR

(Continued on next page)

Table 2. Continued

Author (IRB)	Intervention group treatment	Control group treatment	Evaluation scale	Significance of the intervention group compared with the control group (I/C)	Adverse event (I/C)
Kim et al. (IRB+) [19]	1. HPP	1. N/S (inj.)	1. MoCA-K 2. MMSE-DS 3. K-DRS 4. CDR 5. GDS 6. K-BDI-II 7. STAI 8. STAXI 9. ISI 10. EQ-5D 11. EQ-VAS 12. GQOL-D	1. NS 2. $p = 0.026$ 3–12. NS	1. Likely to be related to the drug: (2 cases/0) 2. Probably not related: (5/5 cases) 3. Definitely not related: (3/4 cases)
Choi et al. (IRB+) [20]	1. HPP 2. Physio	1. N/S (inj.) 2. Physio	1. Residual HFS 2. Mean change in HFS 3. MRS 4. FSH levels 5. E2 levels	1. 9–13 wk: ITT: NS/PP: $p = 0.044$ 2–5. NS	1. SAH: unrelated to HPP 2. Bruise: (8/2) 3. Urticaria: (1/0) 4. Nausea: (1/0) 5. Others: low relevance

Acu, acupuncture; BBS, Berg balance scale; C, control group; CBC, complete blood cell count; CDR, clinical dementia rating; D.I.T.I., digital infrared thermographic imaging; E2, estradiol; EQ-5D, Euro Quality of Life-5 Dimensions; EQ-VAS, Euro Quality of Life-visual analog scale; FSH, follicle-stimulating hormone; GDS, global deterioration scale; GQOL-D, Geriatric Quality of Life scale-Dementia; H/M ratio, H-reflex/M-response ratio; HFS, hot flash score; HM, herbal medicine; HPP, hominis placenta pharmacopuncture; HRV, heart rate variability; I, intervention group; inj., injection; IRB, institutional review board; ISI, insomnia severity index; ITT, intention to treat; K-BDI-II, Korean version of Beck Depression Inventory-II; K-DRS, Korean Dementia Rating Scale; MAS, modified Ashworth scale; MMP, measure of menstrual pain; MMSE-DS, Mini-Mental Status Examination for Dementia Screening; MoCA-K, Korean version of Montreal Cognitive Assessment; MRS, menopause rating scale; MSSL, menstrual symptom severity list; N/S, normal saline; NR, no report; NS, not significant; PA, pharmacopuncture; Physio, physiotherapy; PP, per protocol; SAH, spontaneous subarachnoid hemorrhage; SBV, sweet bee venom; STAI, State-Trait Anxiety Inventory; STAXI, State-Trait Anger Expression Inventory; TUG, time up & go; VAS, visual analog scale; WM, Western medicine.

(2) Reasoning for treatment provided

Excluding Sin et al. [8], 12 RCTs presented reasoning about HPP [9-20], and the evidence was presented based on studies [9-13,15-17,20], books [11,14-18], and protocol study [19] (Table 3).

(3) Extent to which treatment was varied

Clinical trial protocols must choose one of three levels of individualization [21]. Eight RCTs [9-11,13,16,18-20] used pharmacopuncture in both groups. In these groups, pharmacopuncture was performed using the same acupuncture points and pharmacopuncture dosage.

Among the eight RCTs [9-11,13,16,18-20], three [9,10,16] changed other treatments, and 2 [9,16] prescribed herbal medicine differently depending on the patient's pattern identification, and Kim et al. [10] used acupuncture in combination with the symptoms of the mothers (study participants).

Among the RCTs [8,12,14] that added pharmacopuncture to control treatment for the intervention group, two RCTs [8,12] did not specify in detail whether treatment was changed or not, and one RCT [14] specified that herbal medicine was prescribed according to patient's constitution. In two RCTs [15,17], the control group used acupuncture, whereas the intervention group received pharmacopuncture in which both acupuncture and pharmacopuncture were performed on the same acupuncture points. Youn et al. [15] explained that both groups targeted patients with stroke and concurrently received treatment related to stroke. Park et al. [17] used the same physiotherapy standards to both groups (Table 3).

2) Details of needling

(1) Number of needle insertions per subject per session

Excluding the RCT by Sin et al. [8], 12 RCTs [9-20] specified the names of acupuncture points where pharmacopuncture was applied, and the number of needle insertions was confirmed in 11 RCTs [9-16,18-20]. Nine RCTs [10-16,19,20] confirmed the number of needling and specified whether the acupuncture points were unilateral or bilateral. Conversely, two RCTs [9,18] did not

Table 3. Summary of revised STRICTA checklist items 1–2

Author	1. Acupuncture rationale			2. Details of needling				
	1a	1b	1c	2a	2b	2c	2d–f	2g
Sin et al. [8]	Exp: PA	NR	NR	NR	NR	NR	NR	1 mL, Sindongbanguiryo
Park et al. [9]	Exp: HPP	Based on previous studies	ST HM was varied	4	BL2, ST6, ST4, ST2	NR	NR	0.30 × 8 mm, 1 cc, Sinchang Medical
Kim et al. [10]	Exp: PA, HPP	Based on previous studies	ST Acu was varied	3	CV4 Bilateral: BL23	NR	NR	26 G, 1 mL, Seongsim Medical
Kim et al. [11]	Exp-	Based on previous studies and books	ST	7	CV4 Bilateral: ST36, SP9, SP6	As long as the needle	NR	CV4: 26 G, 1/2", 1 mL, Sinchang Medical Bilateral: 30 G, 5/16", 1 mL, Sinchang Medical
Yoo et al. [12]	Exp: PA, HPP	Based on previous studies	NR	2	Bilateral: ST25	NR	NR	NR
Chang et al. [13]	Exp-	Based on previous studies	ST	5	Bilateral: ST25, CV4 Left: ST36, SP10	NR	NR	26 G, 1 mL, Sindongbanguiryo
Yun et al. [14]	Exp: PA, HPP	Based on previous books	ST HM was varied	6	Affected side: Ex-HN1, ST2, ST3, ST4, ST6, TE17	NR	NR	1 mL, Sindongbanguiryo
Youn et al. [15]	Exp: PA, HPP	Based on previous studies and books	ST Stroke Tx was varied	6	Bilateral: GB20, GB12, HT7	NR	NR	29 G, 1 cc, Sinchang Medical
Lee et al. [16]	Exp: PA, HPP	Based on previous studies and books	ST HM was varied	6	Affected side: GB14, SI18, ST4, ST6, TE17, TE23	NR	NR	29 G, 1 cc, Sinchang Medical
Park et al. [17]	Exp: PA, HPP	Based on previous studies and books	ST	NR	BL23, Ex-LE5, GB34, SP10, ST34 Around the knee joint: A-Shi point	NR	NR	Shina Corporation
Noh et al. [18]	Exp-	Based on previous books	ST	5	ST36, GB34, BL55, BL56, BL57	Perpendicular insertion about 1 cm	NR	30 G, 1 mL, Sinchang Medical
Kim et al. [19]	Exp: PA, HPP	Based on previous protocol	ST	4	GV20, CV12 Bilateral: ST36	NR	NR	0.30 × 8 mm, Becton, Dickinson and Company
Choi et al. [20]	Exp: PA, HPP	Based on previous studies	ST	4	CV4, CV6 Bilateral: Ex-BB1	Depth of up to 8 mm	NR	30 G, 1 cc

Acu, acupuncture; Exp, explanation; G, gauge; HM, herbal medicine; HPP, hominis placenta pharmacopuncture; NR, no report; PA, pharmacopuncture; ST, same treatment; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture; Tx, treatment.

specify this aspect; however, the number of needles could be inferred from the amount of pharmacopuncture injection per point and the total amount of pharmacopuncture injected. On the contrary, Park et al. [17] reported the name of the acupuncture points but did not specify whether they were unilateral or bilateral and the total amount of pharmacopuncture injected, so the number of needles was unknown (Table 3).

(2) Names of points used

The acupuncture point where pharmacopuncture was applied and whether it was unilateral or bilateral must be specified [21]. Of the 13 RCTs, 9 [10-16,19,20] specified all of these. The RCT by Sin et al. [8] did not specify the acupuncture point. Although three RCTs [9,17,18] specified the name of the acupuncture point, they did not specify whether it was unilateral or bilateral. Among them, in two RCTs [9,18], whether unilateral or bilateral acupuncture points were used was inferred from the

amount of pharmacopuncture injected per acupuncture point and the total amount injected (Table 3).

(3) Depth of insertion, based on a specified unit of measurement or on a particular tissue level

Three RCTs [11,18,20] specified the insertion depth of pharmacopuncture, the insertion was as long as the needle length [11], perpendicular insertion was approximately 1 cm [18] or up to a depth of 8 mm [20] (Table 3).

(4) Responses sought

No RCTs induced responses such as de qi or muscle twitch (Table 3).

(5) Needle stimulation

Pharmacopuncture cannot be performed needle stimulation techniques or applied with electrical stimulation; thus, no RCTs used such stimulations (Table 3).

(6) Needle retention time

Because pharmacopuncture is usually performed by inserting a syringe into the acupuncture point, injecting the pharmacopuncture solution, and then extracting syringe immediately without needle retention [7], no RCT specified the needle retention time (Table 3).

(7) Needle type

Pharmacopuncture involves injecting the pharmacopuncture solution using a pharmacopuncture injection syringe [1]. Thus, the type of syringe used (gauge, length, capacity, and production company) was checked.

The gauge or length of the syringe needle was specified in nine RCTs [9-11,13,15,16,18-20], and the length was specified in three [9,11,19]. Because the RCT that specified the length also specified the gauge, it appeared that the shape of the syringe needle was specified in terms of gauge or diameter rather than length. As for gauge, 30-gauge was used the most in three RCTs [11,18, 20], 26-gauge in three [10,11,13], and 29-gauge in two [15,16]. Needles with a diameter of 0.30 mm were used in two RCTs [9,19]. Kim et al. [11] used a 26-gauge needle when performing the procedure on CV4 and a 30-gauge for other acupuncture points. Needles with a length of 8 mm (5/16") were used in three RCTs [9,11,19], and 13-mm (1/2") needles were used on CV4 in the RCT by Kim et al. [11].

The capacity of the syringe was determined from 10 RCTs [8-11,13-16,18,20], and the production company was determined from 11 RCTs [8-11,13-19]. Accordingly, most RCTs specified the capacity and manufacturers company of the syringes used. As for the syringe capacity, 1-cc or 1-mL syringes were used in all 10 RCTs [8-11,13-16,18, 20] (Table 3).

3) Treatment regimen

(1) Number of treatment sessions

Excluding two RCTs [8,14], 11 specified the number of treatment sessions. Four RCTs [10,11,13,18] clearly presented the number of treatment sessions. Although the number of treatment sessions was not specified in seven RCTs [9,12,15-17,19,20], it could be inferred from the frequency of treatment and observation period.

The lowest number of treatment sessions was one in RCTs targeting dysmenorrhea [13]. The three RCTs targeting dysmenorrhea [11-13] observed the participants from before the start of the first menstruation to within 2 days of the start of the second menstruation [11] or until the next menstruation [12,13]. In all relevant RCTs [11-13], the observation period was relatively short to accurately determine the effect of pharmacopuncture (Table 4).

(2) Frequency and duration of treatment sessions

Because pharmacopuncture does not require needle retention, only the frequency of treatment was analyzed, excluding the treatment duration. Excluding the RCT by Sin et al. [8], 12 RCTs presented the treatment frequency, with a total of 8 [9,12,13,16-20] with a weekly basis and 2 [14,15] with a daily basis. Kim et al. [10] targeted postpartum discomfort as the target disease and observed the date of birth, and Kim et al. [11] observed the menstrual cycle, with dysmenorrhea as the target disease.

For eight RCTs [9,12,13,16-20] with treatment frequency set to weekly, sessions of two times a week were most frequently implemented in four RCTs [13,16,19,20], 2–3 times a week in two [9,17], three times a week in two [12,16], and five times a week in one [18]. In the two RCTs [14,15], which set the treatment frequency in days, treatment was performed at a frequency of 3 consecutive days [14] and daily [15] (Table 4).

4) Other components of treatment

(1) Details of other interventions administered to the acupuncture group

A total of 10 RCTs [8-10,12-14,16-18,20] employed other interventions in the HPP group. Detailed information on this was provided in all eight RCTs, except for two [8,12].

Table 4. Summary of the revised STRICTA checklist items 3–6

Author	3. Treatment regimen		4. Other components of treatment		5. Practitioner background	6. Control or comparator intervention	
	3a	3b	4a	4b	5	6a	6b
Sin et al. [8]	NR	NR	Acu (Exp-)	NR	NR	NR	Exp-
Park et al. [9]	8–12 sessions	2–3 sessions/wk, for 4 wk	Acu, HM, WM (Exp+)	NR	NR	Based on previous studies To reflect actual clinical treatment	SBV and Acu: in the same way as the intervention group HM, WM (Exp+)
Kim et al. [10]	5 sessions	Days 6, 8, 10, 12, and 13 from the date of birth (day 1)	HM (Exp+)	Consent	Korean medicine doctor resident with > 2 years of clinical experience	Saline injected for blinding	Saline: in the same way as the intervention group Acu (Exp-) HM (Exp+)
Kim et al. [11]	5 sessions	1st, 2nd menstruation: before 3–7 days, within 2 days of starting After the 1st menstruation ends	None	Agreement Prevent pharmacopuncture practitioners from communicating with participants about this clinical study as much as possible	Resident of acupuncture and moxibustion medicine	NR	Saline: in the same way as the intervention group
Yoo et al. [12]	6–12 sessions	3 sessions/wk, for 2–4 wk	Acu (Exp-)	Agreement	NR	Based on previous studies	Exp-
Chang et al. [13]	4 sessions	2 sessions/wk, for 2 wk	Physio (Exp+)	All procedures are performed by one operator Wear an eye patch during the procedure	NR	NR	Saline: in the same way as the intervention group Physio (Exp+)
Yun et al. [14]	NR	For 3 d	Acu, HM, Physio (Exp+)	NR	NR	NR	Acu: in the same way as the intervention group HM, Physio (Exp+)
Youn et al. [15]	5 sessions	1 session/d, for 5 d	None	Agreement	NR	To verify the objective efficacy of HPP	Acu: in the same acupoint as the intervention group
Lee et al. [16]	11–14 sessions	Adm: 3 sessions/wk, for 7–10 d D/C: 2 sessions/wk, for 4 wk	Acu, HM, WM, Physio (Exp+)	NR	NR	Based on previous studies Based on placebo herbal acupuncture study	Saline and Acu: in the same way as the intervention group HM, WM, Physio (Exp+)
Park et al. [17]	6–9 sessions	2–3 sessions/wk, for 3 wk	Physio (Exp+)	NR	NR	NR	Acu: in the same acupoint as the intervention group Physio (Exp+)
Noh et al. [18]	15 sessions	5 sessions/wk	Acu (Exp+)	Consent A translucent tape was attached to the surface of the syringe to blind it	NR	NR	Saline and Acu: in the same way as the intervention group
Kim et al. [19]	16 sessions	2 sessions/wk, for 8 wk	None	Consent A translucent tape was attached to the surface of the syringe to blind it	Korean medicine doctor of neuropsychiatry	NR	Saline: in the same way as the intervention group
Choi et al. [20]	16 sessions	2 sessions/wk, for 8 wk	Physio (Exp+)	Consent A translucent tape was attached to the surface of the syringe to blind it	Experienced Korean medicine doctor	Based on the placebo herbal acupuncture study	Saline: in the same way as the intervention group Physio (Exp+)

Acu, acupuncture; Adm, admission; D/C, discharge; Exp, explanation; HM, herbal medicine; NR, no report; Physio, physiotherapy; SBV, sweet bee venom; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture; WM, Western medicine.

Other interventions administered to the HPP group included acupuncture [8,9,12,14,16,18], herbal medicine [9,10,14,16], physiotherapy [13,14,16,17,20], and Western medicine [9,16] (Table 4).

(2) Setting and context of treatment

Among a total of 13 RCTs, 7 [10-12,15,18-20] enrolled people who consented to clinical research, and among them, four RCTs [10,18-20] mentioned obtaining consent forms. Although the wording of the consent forms was not specified in all RCTs, five [10,11,15,18,19] clearly stated that the experimental content or protocol, such as the purpose and method of the clinical study, was explained to the patients.

In addition, the clinical trial settings were described, for instance, the pharmacopuncture practitioner was prohibited from talking with the participants about this clinical study [11], all participants in all groups wore an eye patch during the procedure [13], blind treatment was applied by attaching translucent tape to the surface of the pharmacopuncture syringe [18-20], etc. (Table 4).

5) Practitioner background

Four RCTs [10,11,19,20] described the background of the practitioners, all of which commonly specified qualifications or affiliations; however, only one RCT [10] described in detail the number of years of acupuncture or other related experience, two [11,19] did not explain this, and one [20] only described it as "experienced" (Table 4).

6) Control or comparator interventions

(1) Rationale for the control or comparator in the context of the research question, with sources that justify the choice(s)

Six RCTs [9,10,12,15,16,20] reported the rationale for the selection of a control or comparison group. Studies [9,12,16] or studies related to control setting [16,20] were presented as references as the sources for choice; however, Kim et al. [10] explained that the purpose was to establish a blind study, and Youn et al. [15] mentioned to verify the objective efficacy of HPP, but did not present evidence such as literature (Table 4).

(2) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for items 1–3 above

For the description of the control or comparison group, components including pharmacopuncture or acupuncture intervention were described in 10 RCTs [9,11,13-20], except for three [8,10,12] that did not explain the details of the acupuncture (Table 4).

7. Adverse event

Among the total of 13 RCTs, 3 [10,19,20] confirmed adverse reactions. One RCT [10] did not report adverse reactions, and two [19,20] reported adverse reactions. Kim et al. [19] explained that two possibly drug-related adverse reactions occurred in the intervention group, 10 reactions were likely not related to the drug, and seven were not related to the drug at all; however, the symptoms were not explained. In the RCT by Choi et al. [20], one case of spontaneous subarachnoid hemorrhage occurred; however, it was not related to the acupuncture, 10 bruises occurred. The study participants were notified in advance, one case of urticaria and mild nausea disappeared after follow-up, and the remaining symptoms were less related to the study and were mild (Table 2).

Ten RCTs [8,9,11-18] did not explain whether adverse reactions were confirmed (Table 2).

8. Treatment results

Four RCTs [12,13,15,16] describe which differences in treatment outcomes between groups were valid in both evaluation scales, 4 [10,18-20] reported that only some were valid, and 4 [8,9,11,17] reported invalid, one [14] revealed unknown difference because treatment effects were not compared between the two groups (Table 2).

9. Research ethics

Of the total 13 RCTs, 3 [10,19,20] were deliberated and approved by the institutional review board (IRB), 9 [8,9,11-17] had no mention of the IRB, and one [18] mentioned that no IRB review was performed.

10. Assessing risk of bias

1) Bias arising from the randomization process

There was no mention of randomization [8,12,14,15], only "random" was specified [10,13,16,17], or a randomization code was used [9,11]. However, all RCTs [8-17] were classified as "some concerns" because no mention was made of whether the allocation sequence was adequately concealed. Three RCTs [18-20] performed randomization using a randomization code [18] or block randomization [19,20], blinding of the operator was performed [18], or an independent statistician generated random numbers and sealed the envelope [19,20], which were all classified as "low risk" (Figs. 2, 3).

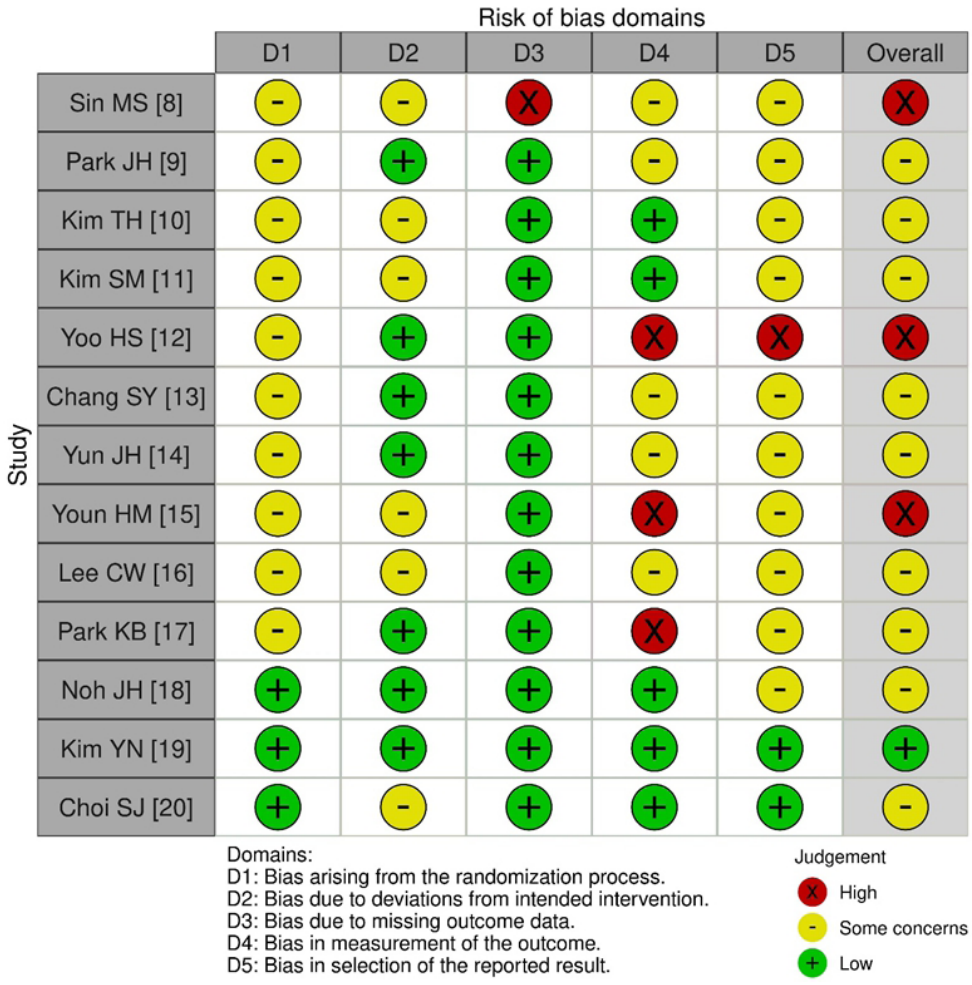

Fig. 2. Risk-of-bias summary.

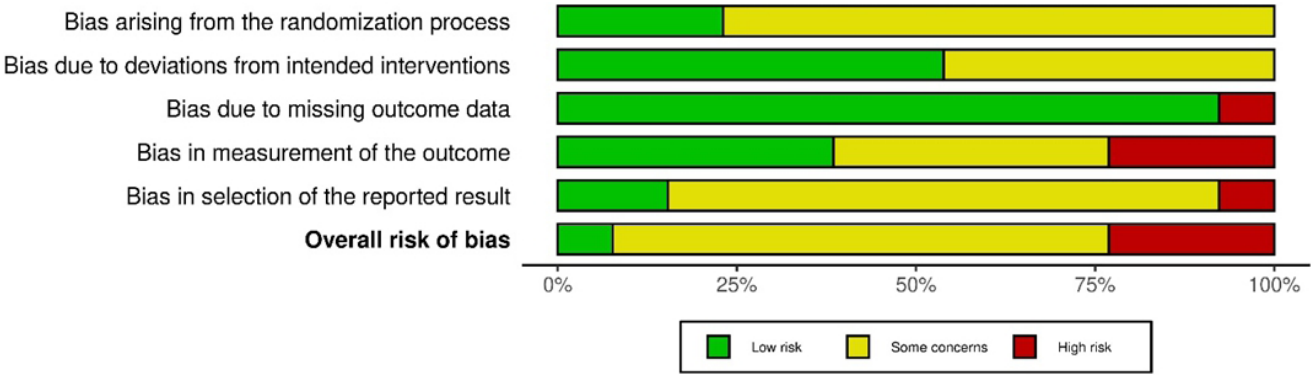

Fig. 3. Risk-of-bias graph.

2) Bias due to deviations from intended interventions

Although no exact information about blinding of study participants was provided [8,10,11,15,16], three RCTs [10,11,16] administered pharmacopuncture in the control group; thus, blinding of the study participants would be possible. Choi et al. [20] mentioned the blinding of the study participants, mentioning that the procedure was performed so that the study participants could not feel

any difference and that the syringes were covered with translucent tape. However, all six RCTs [8,10,11,15,16,20] were classified as "some concerns" because they did not mention the blinding of the intervention provider and the deviation of the intervention.

Although blinding of the study participants and intervention providers was not mentioned, three RCTs [12,14, 17] did not deviate from the intervention. In RCT that specified blinding of study participants, blinding of the intervention providers was not achieved [13], this was not mentioned in one RCT [9], two [9,13] had no participant withdrew from the intervention, and two [18,19] implemented blinding of the intervention, which were all classified as "low risk" (Figs. 2, 3).

3) Bias due to missing outcome data

The RCT by Sin et al. [8] was classified as "high risk" because of missing outcome data in the treatment improvement rate result report, and all other RCTs were classified as "low risk" because they had no missing data (Figs. 2, 3).

4) Bias in measurement of the outcome

In all three RCTs [12,15,17], the outcome assessors were the study participants, and blinding of the study participants was not reported. Because pharmacopuncture was not administered in the control group, blinding of the study participants was unclear, and the intervention results were evaluated using subjective evaluation scales such as the visual analog scale (VAS) or treatment satisfaction. These RCTs were classified as high risk.

In the RCT in which the intervention provider was the outcome assessor, there was no mention of their blinding. However, RCTs that evaluated the intervention results using the House–Brackmann scale [8,14] and Yanagihara's unweighted grading system [9,16] were classified as having "some concerns" because they were not likely to be affected by their knowledge of the intervention. Chang et al. [13] stated that both the study participants and intervention providers were outcome assessors, and both groups administered pharmacopuncture and wore eye patches during the procedure, blinding of the study participants was possible. However, the blinding of the intervention providers was not specified. Although there was a subjective evaluation item, it was classified as having "some concerns" because it also included more objective evaluation items.

Two RCTs performed the same treatment methods, including pharmacopuncture, and likely blinded the study participants [10,11]. One RCT specified the blinding of the study participants [20], and three RCTs [10,11,20] used the evaluation scale, in which the study participants were the outcome assessors. In two RCTs [18,19], the study participants and intervention providers were double blinded. These RCTs were all classified as "low risk" (Figs. 2, 3).

5) Bias in selection of the reported result

Although it is difficult to judge that the results were reported selectively, all RCTs [8-11,13-18] that did not mention the timing of unblinding were classified as having "some concerns."

Yoo et al. [12] measured the results based on a VAS written by the study participants on the day when menstrual pain was most severe, which may more or less depend on the individual. However, the frequency was not reported, and the timing of unblinding was not mentioned, so it was classified as a "high risk."

Two RCTs [19,20], whose results could not be considered to have been selectively reported, were both classified as "low risk" because the statistical analysis was performed by an independent statistician (Figs. 2, 3).

DISCUSSION

Pharmacopuncture is an effective treatment that combines the physical body surface stimulation of conventional acupuncture with the chemical effect of a drug, and the combination of acupuncture site, acupuncture stimulation, and drug infusion can increase and extend the therapeutic effect on the acupuncture points. Pharmacopuncture stimulates meridians and acupuncture points based on the basic theory of Korean medicine, and among modern Korean medicine, it is one of the unique treatments made by combining drug pharmacological action and injection [25]. In addition, pharmacopuncture is being performed in China, Germany, and Italy [1].

Pharmacopuncture is widely used in the field of Korean medicine given its wide range of applications and good therapeutic effect; in particular, HPP was the second most used after bee venom [26]. According to Kang and Kwon [27], microorganisms and precipitated floating matters were not found in Korean medicine extracts, including HPP solution, and in the study analysis conducted by Hong [26], 97.4% of the respondents used pharmacopuncture because it was effective, and the results revealed that some of the patients' physical reactions disappeared naturally, making the use of the pharma-

copuncture solution safe overall.

Evidence-based medicine is also being emphasized in the Korean medicine community; thus, efforts are being made to lay the foundation for establishing the best available evidence, and RCTs are gradually increasing. The number of clinical studies related to Korean medicine has been increasing since 2000; in particular, RCTs are increasingly being published [28], and STRICTA has been prepared in the acupuncture control study to improve the quality of acupuncture clinical research to compensate for problems such as poor understanding of Korean medicine's unique diagnosis and treatment and the reason for acupuncture [5]. Although RCTs are recognized as a reliable research design to properly evaluate the effectiveness of interventions, RCTs with RoB must be evaluated because they can report false effects rather than actual effects [28]. Based on these points, RCTs using HPP published in Korea were reviewed, and STRICTA reporting and bias were evaluated.

HPP RCTs were first published in 2000. By 2022, most RCTs were published in the *Journal of Pharmacopuncture* and *Journal of Korean Acupuncture & Moxibustion Society*, reflecting the characteristics of the pharmacopuncture. Most target diseases were gynecological diseases with five RCTs and peripheral facial paralysis with four. This is all based on the fact that the hominis placenta is warm and nontoxic, and it tonifies qi, blood, and essence, treats diseases related to consumptive disease [29], and contains various factors and hormones [4].

The number of study participants varied from 8 to 128. When conducting research, techniques such as randomization and blinding can be used to reduce bias; however, the number of patients included in the study also affects the research results. Specifically, a very small sample reduces the opportunity to make meaningful discoveries and the generalizability of research results, whereas too large may lead to weak conclusions, and clinically meaningless differences become significant [30]. However, only two RCTs [19,20] performed sample size calculations.

Although the RCT [19,20] that calculated their sample size pointed out that the sample size was small [19] and the sample size calculation was inadequate, they did not consider the effect of stimulating the same acupuncture as in the control group [20]. In addition, most RCTs [9-14,16,18] also mentioned that the sample size was small. Thus, future studies are encouraged to calculate the sample size appropriately. However, difficulty in recruiting many participants due to fear of pharmacopuncture must be considered [10].

Three RCTs [8,12,14] studied the effects of HPP in the intervention group by adding HPP to the control treatment, and eight [9-11,13,16,18-20] performed saline injection [10,11,13,16,18-20] or bee venom [9] in the control group on behalf of HPP in the intervention group, and two RCTs [15,17] performed acupuncture in the control group on behalf of HPP in the intervention group. Thus, in most RCTs, saline injection was set as the intervention of the control group and compared with the effect of HPP in the experimental groups.

Three RCTs [8,12,14] compared the effects of the intervention group in which HPP was added to the treatment of the control group showed no significant difference between the two groups [8,14], or a significant difference in boundary level (p = 0.057) [12]. These RCTs had a few participants (n = 8 [12]; n = 16 [14]) or did not mention patients who were discharged during recovery [8] and they were also pointed out about that in the RCTs.

Among the RCTs that used saline injection [10,11,13,16,18-20] or bee venom [9] as a placebo in the control group, one [13] reported a significant effect in the intervention group compared with the control group, five [10,16,18-20] showed a significant effect in some evaluation scales, and two [9,11] showed no significant difference. They pointed out the lack of study participants [9-11,13,16,18-20], short observation period [9,11,13,16], absence of objective evaluation scales [11], and effects of stimulating the same acupoint [10,11,19]. Among seven RCTs [9-11,16,18-20] that reported some significant differences or did not find differences between the two groups, six [9-11,16,19,20] showed improvement before and after treatment in both groups. Based on this, as Choi et al. [20] mentioned, sample size calculation that also considers the acupuncture point stimulation effect in both groups is necessary, as pharmacopuncture has the combined effect of pharmacological and acupuncture.

Among the two RCTs [15,17] that used acupuncture in the control group instead of the HPP in the intervention group, one [15] showed a significant difference in the intervention group compared with the control group, and one [17] did not find a significant difference between the two groups. In the RCT by Youn et al. [15], which revealed a significant difference, stroke treatment was maintained, and the results may change when reflecting on the analysis patients who dropped out because of delayed treatment and severe sleep disturbances. In addition, both RCTs [15,17] did not specify whether the outcome assessors were blinded, and subjective eval-

uation scales were used. Therefore, implementing blinding and utilizing objective evaluation scales must be actively considered.

Most RCTs mentioned the number of needle insertions or the acupuncture points used. Of these RCTs, they did not specify whether it was unilateral or bilateral. The number of needle insertions can inferred by the amount of injection per point and the total amount of injection only in RCTs [9-11,13,15,16,18] that specified both. In addition, the amount of pharmacopuncture injection should be determined by comprehensively considering the patient's sex, age, disease severity, treatment site, pharmacopuncture type, etc. [2]. The amount of pharmacopuncture solution used should be adjusted according to the situation [25], and based on studies [31,32] reporting that the effect can be affected by the dosage of the pharmacopuncture, both of these must be specified in future studies.

Few RCTs specified the depth of needle insertion, which is thought to reflect that pharmacopuncture does not involve needle retention. Considering that the injection depth is determined based on the site of the acupuncture point and the condition of the lesioned tissue [25] and that clinical studies [33] showed an asymptotic significance in the degree of improvement depending on the depth of pharmacopuncture, future studies specify the depth of needling for pharmacopuncture and conduct research on this, and more significant research results can be derived. In addition, no RCT mentioned the induced response, type of needle stimulation, or time of needle retention. This appears to reflect the characteristics of pharmacopuncture, which involves injecting the pharmacopuncture solution and then withdrawing the needles immediately after injection. In pharmacopuncture, a syringe is used for pharmacopuncture injection, so it cannot be connected to other treatments such as electroacupuncture.

Most RCTs specified the syringe capacity, manufacturers, and gauge or diameter; however, relatively few RCTs specified the length of the syringe needle. Given that only a few RCTs specified the pharmacopuncture depth [11,18,20] and the length of the syringe needle [9,11,19], reflecting that pharmacopuncture does not require needle retention, the length of the pharmacopunture needle must be reported in the future for the same reason as the need for reporting the depth of the needle insertion during acupuncture.

Details of other interventions performed on the HPP group were reported well, and the treatment environment and setting were mentioned. In RCTs that mentioned pretreatment consent, some RCTs explained that the clinical research was sufficiently explained to the participants and they agreed to it; however, they did not present the wording of the consent. Thus, if it is specified, the studies must clearly present what information has been given to the patient and whether participants' voluntary consent was obtained after providing a thorough explanation, particularly in studies involving humans, which is an ethical issue raised from the perspective of protecting the participant [34]. Thus, wording of the consent must be reported in more detail in the future.

The practitioner's background was mentioned only in some RCTs, and these RCTs described qualifications but did not specifically state the number of years of pharmacopuncture experience or other relevant experience, except for Kim et al. [10]. Pharmacopuncture is basically performed by a Korean medicine doctor. However, considering that the background of the practitioner may affect the generalization of clinical trial results, this information must be reported [21] in more detail.

Although descriptions of the control groups or comparator were reported in most RCTs, relatively few RCTs mentioned the rationale for selecting the control or comparator, and among these, some RCTs did not present supporting data. Because employing a control group in experimental studies is effective in minimizing the influence of exogenous variables, application methods are diverse, and results may vary because of interventions [35], specific reporting is imperative.

Among the 17 subitems in the 2010 STRICTA checklist, the report rate for 14 subitems, except for three subitems, which were not reported in all RCTs, reflecting the characteristics of pharmacopuncture mentioned above, was the highest in the RCT by Choi et al. [20] with 13 subitems (92.9%) reported, followed by 12 subitems (85.7%) [10,11], 11 (78.6%) [15,17], 10 (71.4%) [13,16], 9 (64.3%) [14,18], 8 (57.1%) [9], 7 (50.0%) [12,17], and 2 (14.3%) [8], in order of reporting rate of > 50.0% in all RCTs, except the RCT by Sin et al. [8]. In addition, the subitems with a reporting rate of < 50.0% were "depth of insertion, based on a specified unit of measurement or on a particular tissue level," "number of treatment sessions," "practitioner background," and "rationale for the control or comparator in the context of the research question, with sources that justify the choice(s)."

Among the 13 RCTs, three confirmed the occurrence of adverse reactions. Given the small number of RCTs that confirmed adverse reactions and the insufficient description of adverse, drawing conclusion about the safety of

HPP is difficult. Therefore, supplementation in future studies is necessary.

Only three RCTs were reviewed and approved by the IRB, which were published in 2010 [10], 2021 [19], and 2022 [20]. In addition, the RCT [18] that was not reviewed by an IRB was published in 2009, and all RCTs that did not go through IRB screening were published before 2012. This was stipulated through a comprehensive revision in February 2012 that the IRB is a comprehensive research-related management organization that conducts review and education, investigation, and supervision of research plans for not only embryo and genetic research but also human and human-derived material research [36]; through this, it appears that the hospital IRB reflects a change [37] in which researchers who previously went through the IRB voluntarily follow the ethical guidelines of the Helsinki Declaration for publishing research results in academic journals. The ethical conduct of research involving humans is necessary to protect the rights, safety, and welfare of research participants, and IRB review guarantees the ethical initiation and safety of research and its progress and completion [36]; thus, active compliance and reporting are required in the future.

In the RoB assessment, the description of the randomization process was insufficient, including whether it was random or whether factors and allocation order were concealed. In addition, the blinding of the study participants and intervention providers was insufficiently explained. If both groups performed pharmacopuncture, it would be possible to blind the study participants; however, it is necessary to describe the details. In addition, RCTs insufficiently mentioned the timing of unblinding, and in some RCTs, the criteria and frequency of measuring the study results were unclear. The overall RoB was "high risk" in three RCTs, "some concerns" in nine, and "low risk" in one.

In this study, the status of the HPP RCTs was analyzed, and some confirmed the effectiveness of the HPP; however, the number was small, and the effects of various factors such as the size of the study participants, same acupuncture point stimulation effect, etc., could not be excluded. However, this study only targeted domestic RCTs; thus, more meaningful results can be derived if future overseas studies are also conducted.

CONCLUSION

Most domestic RCTs on HPP focused on peripheral facial paralysis or gynecological diseases. Although some of them confirmed the effectiveness of HPP, the influence of various factors could not be ruled out. Most RCTs showed a STRICTA checklist reporting rate of > 50.0%; however, four subitems showed a reporting rate of < 50.0%. Thus, a STRICRA checklist that reflects the characteristics of pharmacopuncture is necessary. Three RCTs received IRB approval, and the overall RoB was mostly "some concerns."

CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

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ETHICAL STATEMENT

This research did not involve any human or animal experiment.

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