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Herbal Medicine for Pediatric Epilepsy: Clinical Research Trends in Traditional Chinese Medicine

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Pediatric epilepsy, a chronic, recurrent brain disorder, is the most common neurological disorder in children. Its prevalence is increasing. Early management is very important since 30～40% of cases persist into adulthood. To provide basic data for future clinical research on pediatric epilepsy using Korean medicine treatment and cooperation between Western medicine doctors and Korean medicine doctors, we reviewed recent clinical research in traditional Chinese medicine (TCM) using herbal medicine for pediatric epilepsy. A total of 23 articles (1 clinical practice guideline, 3 systematic reviews, 15 randomized controlled trials (RCTs), and 4 non-RCTs) were reviewed in this study. The authors summarized characteristics of included studies regarding study subjects, diagnostic tools, pattern identification tools, treatment period, evaluation tools, detail of herbal medicines, treatment effects, and adverse events. Combination therapy using both herbal medicine (HM) and anti-epileptic drugs (AEDs) was performed more frequently than herbal medicine alone. Liver-pacifying medicinal, water-draining medicine, and orifice-opening medicine were frequently used. The main single HMs were Cheonma, Boglyeong, Jogudeung, and Seogchangpo. Combined therapy using HM and AEDs had significant benefits in improving total effective rate. It also appeared to be safer than AEDs. However, since the quality of clinical trials was poor and only studies in the last 10 years were included, the clinical evidence was uncertain. Finally, the authors provided limitations of this study and several suggestions for future research based on our analysis results.

Key Words: Pediatric epilepsy, Herbal medicine, Traditional Chinese medicine, Clinical study, Review

I. INTRODUCTION

Epilepsy, a chronic, recurrent brain disorder, is the most common neurological disorder in children. Currently, approximately 35 million children in the U.S and 54 million children worldwide have epilepsy, and the prevalence of epilepsy is steadily increasing[1]. According to the 2017 health insurance data in South Korea, the prevalence of active epilepsy was 35.4 per 100,000 population[2]. The prevalence among South Korean children was even higher than among adults[3]. Although epilepsy treatment strategies have advanced over time and public awareness of epilepsy has improved, epilepsy has gained increasing national public health interest because chronic seizures can result in serious and persistent health and socioeconomic imbalances, such as a lower quality of life and reduced employment opportunities[1,4]. In a Canadian study, the total health care costs were highest in the first year of life in childhood epilepsy for prediagnosis, initial, and ongoing care than in children without epilepsy[5]. According to the 2010 health insurance data, epilepsy was associated with a significant economic burden due to direct and indirect costs, accounting for approximately 0.64% of the total medical expenses and 0.05% of the gross domestic product in South Korea[6]. Moreover, pediatric patients with epilepsy often encounter challenges in cognition, learning, behavior, and social functions[7]. Furthermore, in 30%~40% of pediatric patients, epilepsy persists into adulthood[8]. As such, the importance of early disease management must not be underestimated.

Pediatric epilepsy is mainly treated pharmacologically using antiepileptic drugs (AEDs). Approximately 30% of patients experience drug-resistant epilepsy, and their seizures persist even when combination therapy of two or more drugs is applied[9]. Generally, medications are discontinued if seizures have not occurred for more than two years. However, seizures recur in approximately 50% of patients within three years of discontinuing medications[10]. Epilepsy is considered in remission when AEDs have ceased for at least five years and seizures have been absent for at least 10 years[11].

The long-term use of AEDs may cause side effects, such as memory impairment, loss of concentration, depression, anxiety, restlessness, sleep disorder, anger, hand tremors, dizziness, and indigestion[12,13]. Serious complications may also arise including liver dysfunction, hematopoietic disorders, renal dysfunction, and irreversible decrease in the visual field[12,13]. Considering these, safer and more effective alternative and complementary therapies than AEDs should be investigated.

Herbal medicine (HM) is one of the key alternative, integrative therapies for children[14]. In East Asia, HM has been used to treat epilepsy for thousands of years[15]. Recent studies have reported the anticonvulsant effects of many herbal medicines and their mechanisms[16-18]. Patients with epilepsy may prefer HMs over other therapies due to their fear of adverse side effects from surgery or AEDs[19]. In a 2008 South Korean study on the use of HMs in pediatric patients with epilepsy, 17.2% of patients reported using HMs concurrently with western medicines and therapies[20].

In traditional Chinese medicine (TCM), symptoms of pediatric epilepsy are infantile convulsions (驚風) and epilepsy (癎症). Infantile convulsions (驚風) frequently appear around the age of one to five years and are characterized by twitches and loss of consciousness. In 『*Soayagjeungjiggyeol* (*小兒藥證直訣*)』, the first medical book for pediatric medicine, infantile convulsions (驚風) were associated with the heart and liver, and many treatment prescriptions were listed[21]. In 『*Dongui Bogam (東醫寶鑑)*』 epilepsy (癎) was classified and treated as fright epilepsy (驚癎), wind epilepsy (風癎), Sig epilepsy (食癎), yang epilepsy

(陽癎), and yin epilepsy (陰癎)[21].

Recent studies in Korean medicine have analyzed the latest related trends in epilepsy and pediatric seizures[22-24]. However, most of these studies were case reports and case series. Moreover, there is a lack of clinical Korean medicine studies in South Korea despite the clinical importance of epilepsy. In contrast, several clinical and experimental studies in TCM on pediatric epilepsy have been published. A previous study investigated the Chinese medicinal trends in pediatric epilepsy but included published studies up to 2013 only. Furthermore, the selection and exclusion criteria were not clearly presented, and the quality of the included studies was not assessed[25]. Therefore, this study aimed to analyze the traditional Chinese medicinal trends in the last 10 years for pediatric epilepsy to provide basic data for future clinical studies on the treatment of pediatric epilepsy using HMs and western-Korean integrated therapies.

II. STUDY PARTICIPANTS AND METHODS

1. Research questions

1) What clinical studies, systematic reviews (SRs), and clinical treatment guidelines (CPGs) on the use of HMs for the treatment of pediatric epilepsy have been published in TCM?

2) What study designs were employed, and what were the study characteristics of the included clinical studies (e.g., participant characteristics, diagnostic tools, pattern identification, treatment duration, effect evaluation tool, safety, and effects)?

3) What types of HMs have been used for treating pediatric epilepsy, and how often were the HMs used?

2. Literature search

The search strategy was as follows. Relevant articles were searched on the Chinese National Knowledge Infrastructure Database, a Chinese literature database. The search terms were limited to the keywords related to the topic, such as "癫痫", "痫病", "痫症", "epilepsy", "seizure", "中药", and "herbal medicine" which were combined using AND and OR to conduct the search (Table 1). Additionally, articles were manually searched in related academic journals, such as the Journal of Pediatrics of TCM (中医儿科杂志) because that includes studies using HM for pediatric epilepsy. The search period was from January 1, 2012, to April 19, 2022.

3. Literature selection and exclusion criteria

Randomized controlled trial (RCT), non-randomized controlled trial (non-RCT), before-after study, SR, and CPG were included. General reviews, case series and case reports, cross-sectional studies, and experimental studies on animals and cells were excluded.

Only studies with children and adolescent participants under the age of 19 years, who were diagnosed with epilepsy, were included. Both genders were included. Participants in studies that provided no clear diagnostic criteria for epilepsy were excluded. Additionally, studies that included participants with other mental disorders (cerebral palsy, mental retardation, attention deficit disorder, autism spectrum disorder, tic disorder, and others) were also excluded.

The treatment of intervention group included HMs or combined therapies using HMs and AEDs. HM preparations included all forms, such as liquids, powders, pills, and capsules. Interventions combined with

Table 1. Searching Strategy

Population (disease)	"癫痫" OR "痫病" OR "痫症" OR "epilepsy" OR "seizure"
Population (age)	"小儿" OR "儿童" OR "幼儿" OR "child"
Intervention	"中药" OR "herbal medicine"

other treatment strategies, such as acupuncture, acupressure, moxibustion, cupping, Chuna therapy, herbal patch, and counseling, were excluded. The treatment of control group included only AEDs. Other control interventions, such as HM, acupuncture, moxibustion, cupping, and counseling, were excluded. We did not limit the evaluation tools.

4. Literature selection

Two individual researchers selected studies (SH Kim and DW Kim). The search results were assessed by each researcher independently and then compared to ensure no relevant studies were omitted. When the researchers' judgments conflicted, a resolution was achieved by discussing the two researchers. The bibliographic information of the searched literature was imported using Endnote X 20 (Clarivate Analytics, Philadelphia, PA, USA). Duplicate articles were removed using the deduplication function of the EndNote program. The articles were then manually evaluated. The titles and abstracts were screened during the first selection process. Subsequently, those articles that failed to meet the selection criteria were excluded in the second selection process. Finally, the full texts of the identified articles were reviewed for inclusion in the study.

5. Data extraction and analysis

Excel 2016 (Microsoft, Redmond, WA, USA) was used by the two researchers (SH Kim and DW Kim) to extract and cross-check the data. The following data were extracted from selected clinical studies: the number of study participants, mean age, disease duration, epilepsy diagnostic criteria, pattern identification, type of HM used, control group intervention type, treatment follow-up period, main outcomes, and adverse events. Data on the type of search sources, number of included studies, search date, protocol registration, total number of included participants, treatment group intervention types, control group intervention types, key evaluation tools, main outcomes, adverse events, and quality evaluation tools were extracted from SR. Additionally, information, such as the development institutions, search histories, quality evaluation tools, evidence evaluation tools, research team compositions, study scopes, and key recommendations, was extracted from CPG. If data were missing, the corresponding authors of the studies were contacted via e-mail to obtain the missing data. If the reviewed contents were inconsistent, the final decision was made by discussing the two researchers.

6. Literature quality assessment

The two independent researchers (SH Kim and DW Kim) evaluated the detailed items of the selected CPG, SR, RCTs, and non-RCTs or before-after study using Appraisal of Guidelines, Research and Evaluation version II (AGREE II) for CPG[26], A measurement tool for the 'assessment of multiple systematic reviews' (AMSTAR) for SR[27], the Cochrane's Risk of Bias (RoB) for RCT[28] and Risk of Bias Assessment Tool for Non-randomized Study (RoBANS) 2.0[29], respectively. AGREE II is the international tool to assess the quality and reporting of practice guidelines. AGREE II can be used in selecting a quality CPG, with a clinician or a team rating a guideline document on the same 23 items to develop a numerical quality score for six domains, making an overall quality rating and a decision on the recommendation of the CPG. AMSTAR is an instrument to assess the methodological quality of SRs. It is a validated tool comprising 11 items and can be answered as "Yes," "No," "Can't answer," or "Not applicable," resulting in scores from 0 to 11. We evaluated the quality of each SR as high when the score was 8~11, moderate when it was 4~7, and low when it was 0~3[30]. Any disagreement was resolved through discussion. RoB evaluation items included

selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and blinding of personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selecting reporting). Each risk of bias was evaluated as high, low, or unclear. The RoBANS evaluated the following six domains regarding risks of bias: selection of participants, confounding variables, measurement of intervention, blinding for outcome assessment, incomplete outcome data, and selective outcome reporting. Each risk of bias was evaluated as high, low, or unclear. Disagreement in the assessed risk of bias between the two researchers was settled through discussions to reach a consensus[28].

7. Data synthesis and analysis

The relative risk (RR) and 95% confidence interval (CI) were assessed for dichotomous variables. As the HM prescriptions, treatment periods, and control groups varied in each included study, there is significant clinical heterogeneity across included studies. We assumed that the true effect size varies from one study to the next and that the studies in our analysis represent a random sample of effect sizes that could have been observed. Therefore, the data were pooled using a random-effects model for post-hoc analysis. Review Manager software version 5.4 (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2020) was used to summarize and synthesize the effect of the studies that provided the same interventions and included the same control groups.

III. RESULTS

1. Literature selection

A total of 204 articles were retrieved through the search. Additionally, nine articles were searched in the Journal of Pediatrics of TCM (中医儿科杂志). As a result, a total of 213 articles were identified. There were no duplications. In the first screening process of the titles and abstracts, studies that failed to meet the selection criteria were excluded, resulting in a total of 44 articles. After reviewing these 44 articles, we excluded conference abstracts (n=2), case reports (n=2), retrospective studies (n=1), studies with no clear description of the epilepsy diagnostic criteria (n=3), studies that were not conducted on children (n=4), and studies that used combinations of different TCM treatment (n=2). As a result, a total of 23 articles (one CPG, three SRs, 15 RCTs, and four before-after studies) were included for analysis (Fig. 1).

2. CPG

One CPG was selected after final screening (Table 2)[31]. The guideline was developed in 2017 by the TCM Association and Tianjin University of Chinese Medicine. In that guideline, studies published until November 2016 were searched using various TCM and related English search databases. RCTs, non-RCTs, and SR were included, and quality evaluation tools were used for the analysis. For the quality of evidence evaluation, *General Principles for the Development of TCM Clinical Guideline* were used[32]. The recommendations were divided into five levels from A to E, according to the type, number, quality of evidence studies, and number of participants. The guideline comprehensively included treatment, definition, diagnosis, TCM pattern identification, and prevention. According to the presenting symptoms, the patterns were divided into fright epilepsy (驚癎), wind epilepsy (風癎), phlegm epilepsy (痰癎), static blood epilepsy (瘀血癎), and deficiency epilepsy (虛癎) in the diagnosis recommendations. For HM (recommendation levels C-D), prescriptions and Chinese patent medicines were recommended according to each pattern. For acupuncture treatment (recommendation level C), the common key acupuncture points, acupuncture points

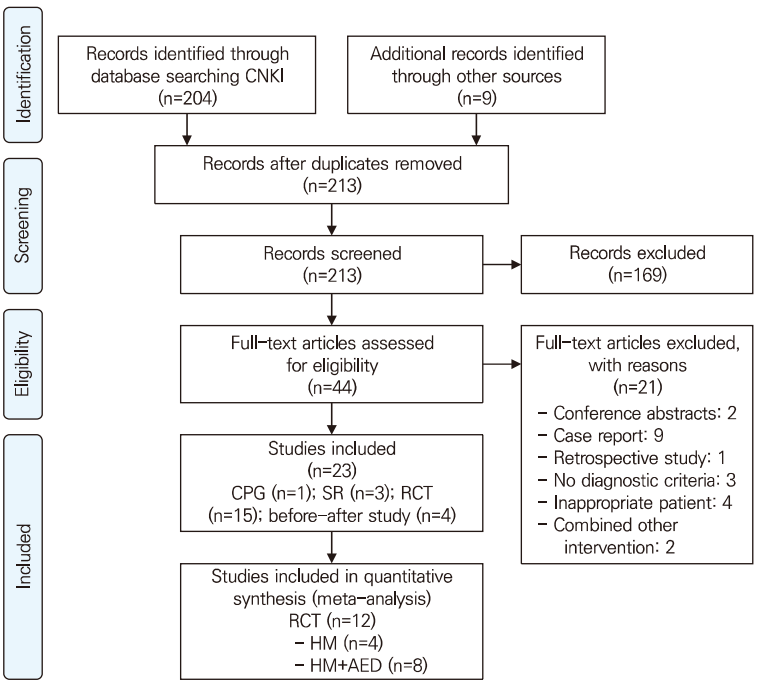

Fig. 1. Flow chart of the study selection process.
AED: antiepileptic drug, CPG: clinical practice guideline, HM: herbal medicine, RCT: randomized controlled trials, SR: systematic review.

for each pattern of epilepsy, needle retaining time, manual technique, and treatment period were presented. The guideline recommended HMs, acupuncture, ear acupuncture, embedding therapy, and moxibustion (recommendation level D). Overall, the level of recommendation was not high, ranging from C to D[31].

3. SR

A total of three SRs were included (Table 3)[33-35]. Of these, the most recent study was by Wang (2016)[33], including articles up to October 2015. Wei (2014)[35] and Wang (2016)[33] used English databases. On the other hand, Li (2014)[35] only searched articles in Chinese databases. The number of RCTs included in the SR ranged from 7 to 17, and all three SR did not register their study protocol. The treatment interventions included HM monotherapies[35], combination therapies of HM and AEDs[34], and combination therapy of HM, AEDs, and acupuncture or moxibustion[33]. The evaluation tools included the total effective rate (TER), number of seizure, duration of seizure, electroencephalography (EEG), and the TCM symptom scale. Meta-analysis of two SRs[33,35] showed that HM monotherapy or HM combined with AEDs significantly improved main outcomes compared with the AEDs group. Li (2014)[35] reported adverse events in only one study among the included studies, and Wang (2016)[33] reported no differences in the adverse events between the control and treatment groups. The quality evaluation tools used in the studies were the Jadad scale[35] and Cochrane RoB[33,34].

4. RCTs and non-RCTs (Tables 4, 5, and 6)

1) General characteristics of study participants

In the 15 RCTs, the number of study participants ranged from 40[36] to 240[37], with an average of ap-

Table 2. The Summary of Included Clinical Practice Guideline

Development year	2017
Development agency	China Association of Chinese Medicine and Tianjin University of TCM
Search strategy	Searched the electronic databases, including CNKI, Wanfang Database, VIP database, MEDLINE, CENTRAL, Clinical Trial, and the National Guideline Clearinghouse, from their inception dates to June 2016
Tool of study quality	Cochrane ROB and Jadad Scale for RCT, MINORS for non-RCT, AMSTAR for systematic reviews
Evaluation tool of evidence	General Principles for the Development of TCM Clinical Guideline
Research team	Working groups of 2015 Guideline for TCM Pediatrics Clinical Diagnosis and Treatment and 2012, 2015 Guidelines for Diagnosis and Treatment of Common Pediatric Diseases in TCM · Epilepsy
Scope	Provides recommendations for the definition, diagnosis, TCM syndrome differentiation, treatment, and prevention of epilepsy in children under 18 years.
The level of evidence	Level I: Large sample*, randomized study, clear results, low false positive or false negative error. Level II: Small sample**, randomized study, inconclusive results, high false positive and/or false negative error. Level III: Non-randomized, contemporaneous controlled studies, and expert consensus based on classic literature. Level IV: Non-randomized, historically controlled, and contemporary expert consensus. Level V: Case reports, uncontrolled studies and expert opinion.
The grade of recommendation	Grade A: Supported by at least 2 Level I studies Grade B: Supported by only 1 level I study Grade C: Only supported by Level II findings Grade D: Supported by at least 1 level III study Grade E: Only supported by level IV or V findings
Major recommendation (diagnosis)	Provides past and family history, clinical symptoms, clinical examination, and differential diagnosis necessary for diagnosing epilepsy in childhood
Major recommendation (TCM diagnosis)	Provides the following five types of TCM syndrome differentiation and symptoms; Fright epilepsy, Phlegm epilepsy, Wind epilepsy, Blood stasis epilepsy, and Deficiency epilepsy
Major recommendation (treatment/herbal medicine)	Modified Zhenjing-wan for fright epilepsy (Recommendation Grade: D) Modified Cheogdam-tang or Mongseog-gondam-hwan for phlegm epilepsy (Recommendation Grade: D) Modified Jeong-gan-hwan for wind epilepsy (Recommendation Grade: C) Modified Tong-gyu-hwalhyeol-tang for blood stasis epilepsy (Recommendation Grade: C) Modified Hageo-palmi-hwan, Yookgunja-tang, Yookmijihwang-hwan, or modified Daejeongpungju for deficiency epilepsy (Recommendation Grade: D) Uigan-hwan, Jeongan-pyeon, Hobag-poryong-hwan, Mongseog-gondam-hwan, Soa-hang-gan-capsule, or Yang-ganpungjeon-hwan (Recommendation Grade: D)
Major recommendation (acupuncture)	Acupuncture treatment (Recommendation Grade: C) - The main acupuncture points include GV26 (Sugu), LR3 (Taechung), GV20 (Baeghoe), GB20 (Pungji), PC6 (Naegwan), ST36 (Zogsamli) Ear acupuncture treatment (Recommendation Grade: D)
Major recommendation (other treatments)	Moxibustion treatment (Recommendation Grade: D) Thread-embedding treatment (Recommendation Grade: C) Also provides prevention and management methods for childhood epilepsy (Recommendation Grade: D)

AMSTAR: assessing the methodological quality of systematic reviews, CNKI: China National Knowledge Infrastructure, MINORS: methodological index for non-randomized studies, RCT: randomized controlled trials, ROB: risk-of-bias tool, TCM: traditional Chinese medicine, TER: total effective rate.
+The recommendation level (or recommendation strength) is divided into five levels: A, B, C, D, and E. Level A is the highest in intensity and decreases in turn.
*High-quality single randomized controlled trial with ≥100 cases or systematic review, **High-quality single RCT with <100 cases or systematic review.

proximately 90 participants. There was one, three-arm study that used two types of HMs[38]. The minimum mean age for the treatment and control groups was 2.4±0.6 and 2.5±0.5 years, respectively[37]. The maximum mean age was 8.74±2.32 years for the treatment group and 8.54±2.57 years for the control group[39]. The duration of epilepsy ranged from one month[36] to nine years[39]. In four non-RCTs, the number of study participants was between 30 and 45, and the minimum and maximum age of the participants was seven months and 18 years, respectively[40]. The duration of epilepsy was reported in only two studies[40,41]. The minimum duration was six months, and the maximum was 13 years[36].

2) Epilepsy diagnosis and pattern identification tools

The detailed diagnosis of epilepsy was available

Table 3. Descriptive Summary of the Included Systematic Reviews

First author (year)	Databases	Number of included studies	Searching date (month /date/year)	Study design of included studies	protocol	Total number of participants	(A) Type of intervention group	(B) Type of control group	Main outcomes	Main findings	Adverse events rates	Study quality assessment tools
Li (2014)	CBM CNKI VIP Database Wanfang Database	12	NR/NR/ 2013	RCT	NR	60～200 participants per study	HM combined with AEDs	AEDs	①TER ②Number of convulsions ③Seizure frequency ④Improve on EEG	① (A)＞(B)$^{+}$ ② (A)＜(B)$^{+}$ ③ N.S ④ (A)＞(B)$^{+}$	Only one study reported adverse events	Jadad Scale
Wei (2014)	CBM CENTRAL CNKI EMBASE MEDLINE VIP Database Search on Google, Baidu	7	01/NR/ 2013	RCT	NR	819	HM	AEDs	①TER	① (A)＞(B)$^{+}$	NR	Cochrane risk-of-bias tool
Wang (2016)	CBM CENTRAL CNKI EMBASE MEDLINE VIP Database Wanfang Database	17	10/31/ 2015	RCT	NR	2895	HM monotherapy or HM combined with AEDs, AT, or MT	AEDs	①TER ②Improve on EEG ③Reduce the EEG focal discharge frequency ④Reduce the EEG focal discharge area ⑤Seizure frequency ⑥Seizure duration ⑦TCM syndrome scores	① (A)＞(B)$^{+}$ ② (A)＞(B)$^{+}$ ③ (A)＞(B)* ④ (A)＞(B)$^{+}$ ⑤ (A)＜(B)$^{+}$ ⑥ (A)＜(B)$^{+}$ ⑦ N.S	N.S	Cochrane risk-of-bias tool

AEDs: antiepileptic drugs, AT: acupuncture treatment, CBM: Chinese biology medical, CNKI: China National Knowledge Infrastructure, EEG: electroencephalogram, HM: herbal medicine, MT: moxibustion treatment, RCT: randomized controlled trials, TCM: traditional Chinese medicine, TER: total effective rate.
'*' and '+' mean significant differences between two groups, $p<0.05$ and $p<0.01$, respectively. 'N.S' means no significant difference between two groups, $p>0.05$.

Table 4. The Characteristics of Included Randomized Controlled Trials

First Author (year)	Sample size (intervention:control) (included→analyzed)	Mean age (range) (years)	Duration of illness	Epilepsy type (diagnostic criteria)	Pattern identification (diagnostic criteria)	(A) Treatment intervention	(B) Control intervention	Treatment duration	Outcome and results (post-treatment)
Chen (2012)	62 (36:26)→ 62 (36:26)	(A): 4.8 (B): 4.9	6 months (mean)	NR (RCEESC)	NR	HM, Antiepileptic drugs	Antiepileptic drugs	6 months	① TER: (A) > (B)*
Kuang (2012)	78 (39:39)→ 68 (34:34)	(A), (B): 5.31±10.53	>24 months	Primary generalized seizure (CDTEDSTCM, CEILAE)	NR	HM, Valproate	Valproate	NR	① TER(remission rates): (A) > (B)*
Ma (2012)	120 (60:60)→ 120 (60:60)	(A), (B): 7.4±1.2	0∼3 years	NR (EEG)	NR	HM, Antiepileptic drugs	Antiepileptic drugs such as Carbamazepine, Phenobarbital, Primidone, Clonazepam, or Phenytoin	NR	① TER: (A) > (B)*
Rong (2012)	100 (NR)→ 91 (31:30:30)	NR	NR	Tonic-clonic seizure (Pediatrics)	Kidney essence deficiency, Wind-phlegm block pattern (CDTEDSTCM)	(A): HM (B): HM	(C): Carbamazepine 10∼20 mg/(kg·d)	1 year	① TER (based on clinical symptoms and EEG): N.S ② TER (based on TCM syndrome scores): (A) > (C)*, (B) > (C)* ③ Cognitive function: (A) > (C)*, (B) > (C)* ④ TER (based on IQ): (A) > (B)*, (A) > (C)* ⑤ Verbal IQ, Performance IQ, Full scale IQ: (A) > (B)*, (A) > (C)*
Kong (2013)	124 (62:62)→ 124 (62:62)	(A), (B): 6.1±2.3	6∼22 months	Various types of epilepsy (CEILAE)	NR	HM, Antiepileptic drugs	Antiepileptic drugs	2 months	① Seizure frequency: (A) < (B)* ② TER: (A) > (B)*
Qi (2013)	40 (20:20)→ 40 (20:20)	(A): 5.2 (B): 5	1∼19 months	NR(RCEESC)	NR	HM, Antiepileptic drugs	Antiepileptic drugs such as Phenobarbital, Clonazepam, Phenytoin, or Valproate	6 months	① TER: (A) > (B)*
Yao (2014)	70 (35:35) → 65 (31:34)	(A): 7.6±1.7 (B): 7.4±1.6	(A): 6.4± 2.7 months (B): 6.5± 2.6 months	NR (EEG)	NR	HM, Antiepileptic drugs	Antiepileptic drugs such as Carbamazepine, Phenobarbital, Primidone, or Valproate	6 months	① TER: (A) > (B)* ② Seizure frequency: (A) < (B)+ ③ Patient compliance: (A) > (B)*
Zheng (2014)	64 (32:32) → 64 (32:32)	(A): 6.2±4.5 (B): 6.9±4.8	NR	NR (PCM)	Wind epilepsy, Phlegm epilepsy, Fright epilepsy, or Blood stasis epilepsy (PCM)	HM	Topiramate and Valproate	1 year	① TER: N.S

Table 4. Continued 1

First Author (year)	Sample size (intervention:control) (included→analyzed)	Mean age (range) (years)	Duration of illness	Epilepsy type (diagnostic criteria)	Pattern identification (diagnostic criteria)	(A) Treatment intervention	(B) Control intervention	Treatment duration	Outcome and results (post-treatment)
Yang (2015)	72 (36:36) → 69 (34:35)	(A): 6.4±0.6 (B): 6.9±0.6	1～5 years	Absence seizure (Practical pediatric epilepsy)	Phlegm epilepsy (GDTCDPTCM)	HM	Valproate 60～90 mg/(kg·d)	1 year	① TER(based on clinical symptoms): N.S ② TER (based on seizure frequency): (A)＞(B)* ③ TER (based on TCM syndrome scores): (A)＞(B)*
He (2016)	58 (29:29) → 58 (29:29)	(A): 6.8±2.2 (B): 6.6±2.4	1 month～8 years	NR (CEILAE)	NR	HM	Valproate 5～10 mg/(kg·d)	NR	① TER: (A)＞(B)* ② Adverse event rates: (A)＜(B)*
Zhang (2017)	80 (40:40) → 80 (40:40)	(A): 5.41±2.39 (B): 5.49±2.43	(A): 22.31±11.33 months (B): 21.21±10.18 months	Primary epilepsy (CEILAE)	Wind-phlegm block pattern (CDTEDSTCM)	HM, Valproate 10～30 mg/(kg·d)	Valproate 10～30 mg/(kg·d)	1 year	① TER: (A)＞(B)* ② Seizure frequency: (A)＜(B)* ③ Seizure duration: (A)＜(B)* ④ Improve on EEG: (A)＞(B)*
Hou (2018)	240 (120:120) → 240 (120:120)	(A): 2.4±0.6 (B): 2.5±0.5	1 month ～ 4 years	NR (CEILAE)	NR	HM, Valproate 20 mg/(kg·d)	Valproate 20 mg/(kg·d)	1 year	① TER: (A)＞(B)* ② Seizure frequency: (A)＜(B)*
Zhang (2019)	60 (30:30) → 60 (30:30)	(A): 8.53±0.24 (B): 8.54±0.26	NR	NR (CCMD3)	NR	HM, Valproate 20～30 mg/(kg·d)	Valproate 20～30 mg/(kg·d)	3 months	① TER: (A)＞(B)* ② Adverse event rates: N.S
Huang (2020)	100 (50:50) → 84 (44:40)	(A): 4.5±0.7 (B): 4.4±0.8	1～24 months	Tonic-clonic seizure (Clinical practice guidelines for the diagnosis and treatment of epilepsy)	Phlegm turbidity obstructing the orifices (PCM)	HM, Valproate 20～40 mg/(kg·d)	Valproate 20～40 mg/(kg·d)	3 months	① TER: (A)＞(B)* ② TCM symptom standard: (A)＜(B)* ③ Peripheral blood IgA, IgG, IgM: (A)＞(B)* ④ Th17, IL-6, IL-17A, hs-CRP, Hcy levels: (A)＜(B)* ⑤ Adverse event rates: (A)＜(B)*
Qi (2021)	90 (45:45) → 90 (45:45)	(A): 8.74±2.32 (B): 8.54±2.57	1～9 years	NR (Diagnosis epilepsy in children, Pediatrics of practical traditional chinese medicine)	NR	HM, Oxcarbazepine 8～10 mg/(kg·d)	Oxcarbazepine 8～10 mg/(kg·d)	6 months	① TCM syndrome scores: (A)＜(B)* ② WISC, WMS: (A)＞(B)* ③ NPY, NGF: (A)＜(B)*

CCMD: Chinese classification of mental disorders, CDTEDSTCM: criteria of diagnosis and therapeutic effect of disease and syndromes in traditional Chinese medicine, diagnostic criteria for internal diseases; CEILAE: classification of the epilepsies of international league against epilepsy, EEG: electroencephalogram, GDTCDPTCM: guidelines for diagnosis and treatment of common diseases of pediatrics in traditional Chinese medicine, GCTNCM: guidelines for clinical trials of new Chinese medicines, Hcy: homocysteine, HM: herbal medicine, hs-CRP: high-sensitivity C-reactive protein, Ig: immunoglobulin, IL: interleukin, IQ: intelligence quotient, NGF: nerve growth factor, NPY: neuropeptide Y, NR: none reported, PCM: pediatrics of Chinese medicine, RCEESC: recommendations for the classification of epilepsy and epilepsy syndromes in children, TER: total effective response, Th: helper T cells, WISC: Wechsler Intelligence Scale for Children, WMS: Wechsler Memory Scale.
'*' and '+' mean significant differences between the two groups, $p<0.05$ and $p<0.01$, respectively. 'N.S'means no significant difference between thetwo groups, $p>0.05$.

Table 5. Thecharacteristics of Included Non-Randomized Controlled Trials

First Author (year)	Sample size (intervention:control) (included→analyzed)	Mean age (range) (years)	Duration of illness	Epilepsy type (diagnostic criteria)	Pattern identification (diagnostic criteria)	Treatment intervention	Outcome	Treatment duration/ Follow-up	Outcome and results (post-treatment)
Zou (2012)	45	7～13 years	6～73 months	Various types of epilepsy (CEILAE, GCTNCM)	Wind epilepsy, Phlegm epilepsy, Fright epilepsy, or Blood stasis epilepsy (NR)	HM or HM+ antiepileptic drugs	① TER	2 years	Cure: 10 Markedly improved: 13 Improved: 11 Invalid: 11
Cao (2016)	30	7 months～ 18 years	0.5～13 years	NR (Diagnosis and evaluation standard for epilepsy)	Wind epilepsy, Phlegm epilepsy, Fright epilepsy, or Blood stasis epilepsy (NR)	HM or HM+ antiepileptic drugs*	① Seizure frequency ② Seizure severity ③ Seizure duration ④ Total symptomatic scores ⑤ TER ⑥ Improve on EEG	1 year	①, ②, ③, ④: Post-treatment: improved ($p<0.01$) ⑤ Cure: 7 Markedly improved: 12 Improved: 9 Invalid: 2 ⑥ Improved: 7 Invalid: 2
Tan (2018)	41	8.05±1.64	NR	Refractory status epilepticus	NR	HM and antiepileptic intravenous drugs	① TER ② Adverse event rates	24 hours	① Improved: 30 Invalid: 11 ② 24.39% (10/41)
Xie (2018)	30	NR	NR	NR (Pediatrics of Chinese medicine)	NR	HM	① TER	3 months	Cure: 25 Improved: 3 Invalid: 2

EEG: electroencephalogram, GCTNCM: guidelines for clinical trials of new Chinese medicines, HM: herbal medicine, CEILAE: classification of the epilepsies of international league against epilepsy, NR: none reported, TER: total effective response.
*If the patient does not take anticonvulsant drugs, administer HM alone. If the patient takes anticonvulsant drugs, a combination treatment of herbal medicines and anticonvulsants is performed.

Table 6. Adverse effects of Included Study

	Herbal medicine	Antiepileptic drugs
Chen (2012)	None [HM+AEDs]	Erythema 3
Kuang (2012)	NR [HM+AEDs]	NR
Ma (2012)	NR [HM+AEDs]	NR
Rong (2012)	NR [HM]	NR
Kong (2013)	NR [HM+AEDs]	NR
Qi (2013)	None [HM+AEDs]	None
Yao (2014)	NR [HM+AEDs]	NR
Zheng (2014)	None [HM]	Gastrointestinal discomfort 2, dizziness 2, headache 1, weight change 1
Xue (2015)	Gastrointestinal discomfort 2, sleepiness 1, Weight gain 3, etc. 2 [HM+AEDs]	Gastrointestinal discomfort 5, sleepiness 6, Weight gain 3, etc. 4
Yang (2015)	NR [HM]	NR
He (2016)	None [HM](36, 46, 47, 50)	Headache 1, dizziness 2, nausea and vomiting 2
Zhang (2017)	NR [HM+AEDs]	NR
Hou (2018)	NR [HM+AEDs]	NR
Zhang (2019)	Sleepiness 1 [HM+AEDs]	Sleepiness 1, gastrointestinal discomfort 1
Huang (2020)	Sleepiness 3, forgetfulness 1, gastrointestinal discomfort 3, liver damage 3 [HM+AEDs]	Sleepiness 2, forgetfulness 4, gastrointestinal discomfort 8, liver damage 5
Qi (2021)	NR [HM+AEDs]	NR
Zou (2012)	Mild elevation of transaminase 11, loose stools 17 [HM or HM+AEDs]	N.A
Cao (2016)	NR [HM or HM+AEDs]	N.A
Tan (2018)	Altered consciousness 1, nausea and vomiting 1, language disorder 2, dull 3, lethargy 3 [HM+AEDs]	N.A
Xie (2018)	None [HM]	N.A

AEDs: antiepileptic drugs, HM: herbal medicine, NR: not reported, N.A: not applicable.

only in six studies[38,42-45]. The most used epilepsy diagnostic tool was the Classification of the Epilepsies of the International League Against Epilepsy[11]. Other tools included recommendations for the classification of pediatric epilepsy, TCM standard of diagnostic treatment, practical pediatric epilepsy diagnosis, TCM classification of mental disorders, CPGs for epilepsy diagnosis and treatment, practical TCM-pediatrics, and EEG. Five studies performed pattern identification as follows: kidney essence depletion(腎精虧損)/wind-phlegm obstruction (風痰閉阻)[38], fright epilepsy (驚癎)/phlegm epilepsy (痰癎)/wind epilepsy (風癎)/static blood epilepsy (瘀血癎)[40-42], phlegm epilepsy (痰癎)[43], wind-phlegm obstruction (風痰閉阻)[44] and phlegm clouding the orifices (痰濁蒙竅)[45].

3) Evaluation tools

The main evaluation tool was the TER. Other tools included assessment of seizure frequency, the TCM symptom scale, cognitive functions, and patient compliance (Table 4). Additionally, objective evaluation tools, such as EEG[44], neurotrophic factors[39], immunity and inflammation levels in the blood[45], were also assessed. In most studies, the TER was calculated as a percentage out of 100% after dividing the total number of patients in the cured (全癒), significantly improved (顯效), and improved groups. In a study by Xie[46], the TER was evaluated at three levels: cured (absence of symptoms), significantly improved (more than 50% of symptoms resolved), and no improvement (less than 50% of symptoms resolved). The TER evaluation criteria differed between the selected studies. Most studies[36-38,40-44,47-52] used TCM's new guidance principles and evaluated the TER at four levels: cured (no seizure for more than a year, EEG recovered to a normal level), significantly improved

(seizure frequency reduced by more than 75% or no seizure for more than six months , EEG significantly improved), improved (seizure frequency reduced by 50～75%, EEG improved), and no improvement (seizure frequency reduced by less than 50%, no improvement or worsening of seizure frequency, severity, symptoms, and EEG)[53]. In contrast, Huang (2020) evaluated the TER at four different levels: significant improvement (seizure frequency reduced by more than 75%), improvement (seizure frequency reduced by 50～75%), slight improvement (效差, seizure frequency reduced by 25～50%), and no improvement (seizure frequency reduced by less than 25%)[45]. In another study by Ma[54], the TER was assessed as follows: cured (complete suppression of seizures, no seizures during two years of follow-up), significant improvement (seizure duration, symptoms, and frequency reduced by more than 60%, improvement persisted for more than two years), improvement (seizure duration, symptoms, and frequency reduced by less than 50%, improvement persisted for less than two years), and no improvement (no clear changes in seizures). Tan[55] intravenously administered AEDs and HM (Angungwoohwang-hwanhuang-wan) in patients with treatment-resistant epilepsy with uncontrolled seizures. Reduction in seizures was evaluated at 2, 6, 7, 12, and 24 hours after administration. More and less than 50% reduction in seizures was evaluated as improvement and no improvement, respectively.

Huang[45] used TCM symptom standard in the TCM CPGs for pediatric epilepsy[31]. This scale measured the duration of clouded consciousness (one point for less than 30 minutes, two points for 30 minutes to one hour, three points for one to three hours, and four points for more than three hours), severity and duration of spasticity and convulsions (spasticity: one point for less than a minute, two points for one to five minutes, three points for five to 10 minutes, and four points for more than 10 minutes; convulsions: one point for less than three minutes, two points for three to 10 minutes, three points for 10 to 30 minutes, and four points for more than 30 minutes), and changes on EEG (one point for mild abnormality, two points for moderate abnormality, and three points for severe abnormality). The scores of the four results were summed up to evaluate the improvement of epilepsy.

4) HM treatment

Of the selected 15 RCTs, four studies provided HM monotherapy[38,42,43,50], while the remaining 11[36,37,44,45,47-49,51,52,54] provided a combination of HM and AEDs. In the selected four non-RCTs, a combination of HMs and AEDs was employed[40,55], and the two other non-RCTs provided HM monotherapy[41,46]. In one of the studies that provided combination treatment, AEDs were administered intravenously to patients with treatment-resistant epilepsy[55].

The prescription, dosage form, and ingredients of HM provided to the treatment groups were analyzed (Appendix 1). In 11, 4, 2, and 2 of 19 studies, decoction, pills, granules, and capsules were used, respectively. Various prescriptions, including Seongsin-yugan-tang (醒神愈癇湯), Hwatag-haedog-jogan-tang (化濁解毒調肝湯), Cheogdam-tang (滌痰湯), Jingyeong-hwan (鎭驚丸), Jeong-gan-hwan (定癇丸), Tong-gyu-hwalhyeol-tang (通竅活血湯), Ansin-jeong-gan-tang (安神定癇湯), Cheogdam-jeong-gan-tang (滌痰定癇湯), Yookgunja-tang (六君子湯), Sikgyung-tang (熄痙湯), Padubunho-hwan (巴豆粉糊丸), and Jeong-gan-san (定癇散), were used. Additionally, Chinese patent medicines, such as Jeong-gan-hwan (定癇丸加味方), Hangjeongan capsule (抗癲癇胶囊), Yongchang capsule (茸菖), and Angung-woohwang-hwan (安宮牛黃丸), were used as well. Pattern identification was provided in three studies[40-42], and basic medicinal therapies were adjusted according to the presenting symptoms in four studies[44-46,50].

A total of 101 types of ingredients were used as

HMs (Appendix 2). HM ingredients that were used more than 10 times included Gastrodia elata (天麻), Poria cocos (茯苓), Uncaria sinensis (釣鉤藤), and Acorus gramineus (石菖蒲). Gastrodia elata was used the most in 14 different HMs. Other key ingredients were as follows: Buthus martensii (全蝎), Batryticatus Bombyx (白僵蠶), and Pinellia ternata (半夏) were used nine times, and Curcuma wenyujin (鬱金) was used eight times. Sculellaria baicalensis (黃芩), Salvia miltiorrhiza (丹蔘), Arisaema amurense (牛膽南星), Glycyrrhizae uralensis (甘草), Polygala tenuifolia (遠志), and Paeonia lactiflora (芍藥) were used seven times, and Liriope platyphylla (麥門冬), Citrus unshiu (陳皮), and Pericaeta communisma (地龍) were used six times. Additionally, Atractylodes japonica (白朮), Pteria margaritifera (珍珠母), and Angelica gigas (當歸) were used five times. Each ingredient was classified according to the treatment guidelines of TCM. Liver-pacifying medicinal (平肝藥), Water-draining medicinal (利水藥), and orifice-opening medicinal (開竅藥) were used often. Other types of ingredients were also used (Appendix 3).

5) Control group treatment

In six studies, various AEDs were provided to the control group. In nine studies, a single AED was used. Of the drugs used for monotherapy in the control group, valproate was administered in seven studies[37,43-45,50-52], and carbamazepine and oxcarbazepine were administered in one study each[37,43-45,50-52].

6) Treatment and follow-up periods

The treatment period ranged from two months[48] to two years[41]. The most common treatment duration was one year[37,38,42-44]. The mean treatment period of the selected studies was 8.33 months. In three studies, the treatment duration was not indicated. No study followed up with the participants after the treatment period. In a study by Tan[55], AEDs were administered intravenously with a HM (Angungwoohwang-hwan) in patients with treatment-resistant epilepsy for 24 hours to evaluate the convulsion suppression effects.

5. Evaluation of study quality

The quality of included CPG is generally insufficient (Appendix 4). Included CPG did not report many domains, including rigour of development, clarity of presentation, applicability, editorial independence, and so on. All SRs were considered medium quality (5~7 points)[33-35]. There are no registered study protocols in the all SRs before conducting the SRs. All included SRs presented a list of included studies but did not provide a list of excluded studies. All studies assessed the methodological quality of the included studies. One study did not use the scientific quality of included studies in formulating conclusions appropriately[33]. All studies evaluated the likelihood of publication bias and did not state conflicts of interest (Table 7).

The risk of bias was evaluated for RCTs. A "low" risk of selection bias for random sequence generation was assigned to five studies that used a random number table for random assignment[38,43-45,50]. Those studies that assigned participants according to the chronological order of admission without using a random number table were assigned a "high" risk of selection bias for random sequence generation[37,49,51]. Other studies that had no description regarding the random assignment method were assigned an "unclear" risk of selection bias for random sequence generation. For allocation concealment, one study that used the envelope method after a random assignment was evaluated as having a "low" risk of bias[45]. Regarding performance bias, all studies were evaluated to have a "high" risk of performance bias as blinding was impossible due to the nature of the interventions. For detection bias, one study that described blinding of all researchers and evaluators of the study was assigned as having a "low" risk of

Table 7. AMSTAR Checklist Assessment of the Included Reviews

Study ID	Li (2014)	Wei (2014)	Wang (2016)
(1) A priori design	No	No	No
(2) Duplicate study selection and data extraction	Can't answer	No	No
(3) A comprehensive literature search	No	Yes	Yes
(4) Status of publication used as an inclusion criterion	No	Yes	Yes
(5) A list of included and excluded studies	No	No	No
(6) Characteristics of the included studies	Yes	Yes	Yes
(7) Quality assessed and documented	Yes	Yes	Yes
(8) Quality used appropriately in formulating conclusions	Yes	Yes	No
(9) Methods for combining the findings appropriate	Yes	Yes	Yes
(10) Likelihood of publication bias assessed	Yes	Yes	Yes
(11) Conflicts of interest stated	No	No	No
Overall quality assessment	Medium (score of 5)	Medium (score of 7)	Medium (score of 6)

AMSTAR: assessing the methodological quality of systematic reviews.

bias[45]. Studies with no missing values were evaluated as having a "low" risk of attrition bias. Additionally, those studies with missing values but had a similar number of participants who dropped out in both groups were assigned a "low" risk of attrition bias. In contrast, two studies with significant missing data were assigned a "high" risk of attrition bias[45,49]. All studies had an "unclear" risk of selective reporting bias as there were no descriptions that the studies were conducted according to the protocols. For other biases, heterogeneity in demographic characteristics was assessed, and all studies had a "low" risk of bias (Fig. 2).

The risk of bias was also evaluated in non-RCT studies. No studies had a "high" risk of bias for the selection of participants and incomplete outcome data. In two studies[40,41], a confounding variable of confusion between HM monotherapy and a combination treatment of AED and HM was observed. Therefore, these two studies were assigned a "high" risk of bias for confounding variables. In a study by Xie[46], the treatment period was inaccurate, and a "high" risk of bias for intervention measurement was assigned. No studies described the blinding of the evaluator. Therefore, all studies were evaluated to have an "unclear" risk of bias for blinding outcome assessment. Additionally, all studies were assigned an "unclear" risk of bias for selective outcome reporting as there were no descriptions that the studies were conducted according to the protocol (Fig. 3).

6. Treatment effects

Meta-analysis was conducted in 12 RCTs (four[38,42,43,50] and eight RCTs[36,37,44,45,47-49,51,52] that provided monotherapy and combination treatment, respectively) that used the TER to assess the treatment effects. Sub-group analysis was performed according to the treatment period (more or less than six months). In a meta-analysis of eight studies[36,37,44,45,47-49,51,52] that provided combination treatment (n=1088), the HM and AED combination treatment group showed significantly improved TER compared with the AED monotherapy control group (RR: 1.22, 95% CI: 1.15 to 1.29, $p<0.00001$, $I^2=29\%$). Sub-group analysis according to the treatment period showed no significant differences in the treatment effects. In a meta-analysis of four studies[38,42,43,50] that provided monotherapy (n=252), the HM treatment group showed improved TER compared with the AED monotherapy control group. Nevertheless, the result was not significant (RR: 1.09, 95% CI: 0.99 to 1.20, p=0.08, $I^2=0\%$). In a subgroup analysis according to the treat-

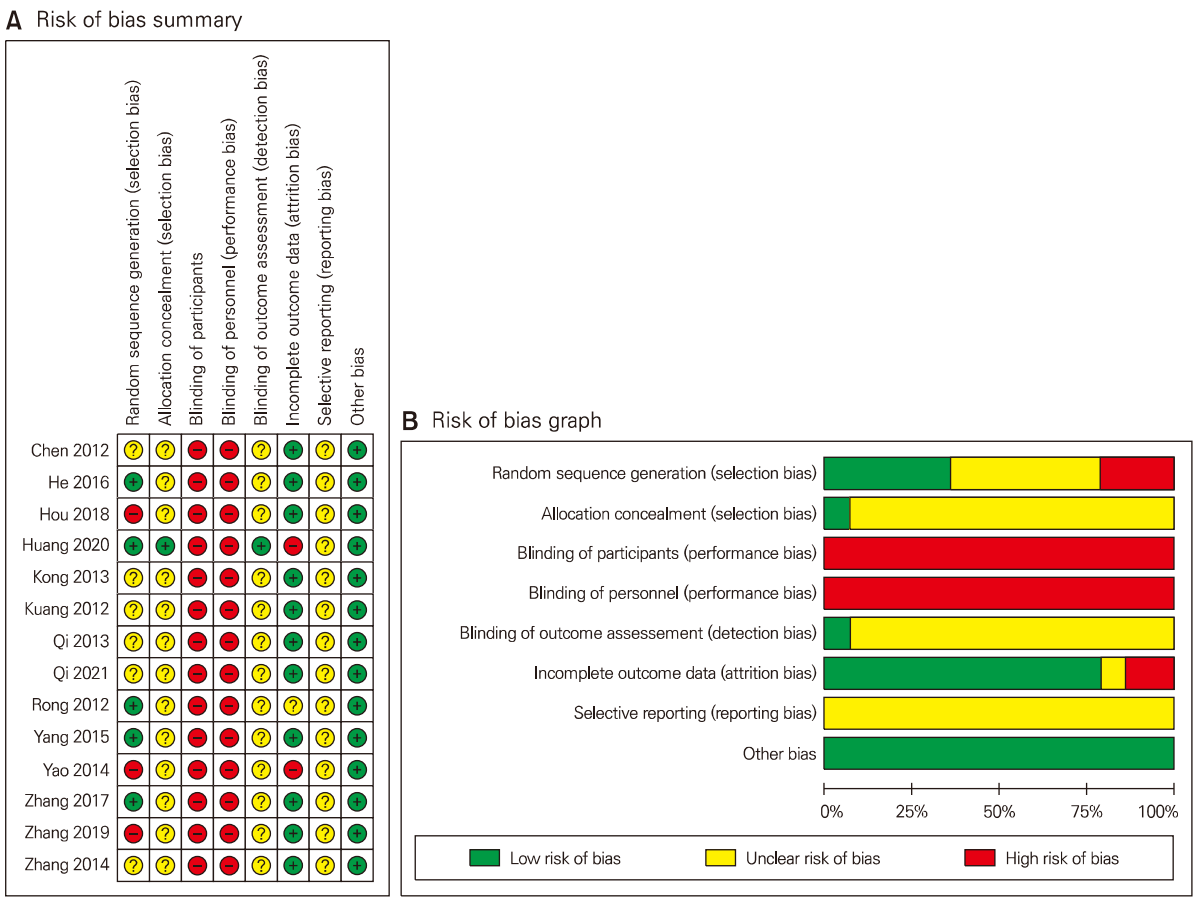

Fig. 2. (A) Risk of bias summary. Low, unclear, and high risk, respectively, are represented with the following symbols: "+", "?", and "-". (B) Risk of bias graph. Review of authors' judgments about each risk-of-bias item presented as percentages.

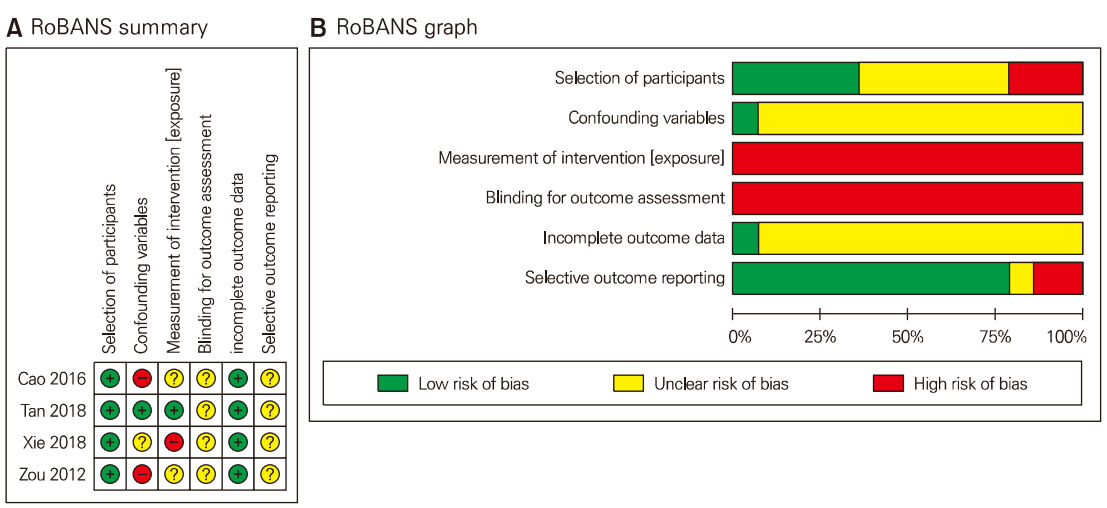

Fig. 3. (A) RoBANS summary. Low, unclear, and high risk, respectively, are represented with the following symbols: "+", "?", and "-". (B) RoBANS graph. Review of authors' judgments about each risk-of-bias item presented as percentages.
RoBANS: Risk of Bias Assessment tool for Non-randomized Study.

ment period, one study[50] with a treatment period of less than 6 months showed more significant effects than studies with a treatment period of more than 6 months (Fig. 4). In the study of Zhang (2017)[44], combination treatment with HM and AED significantly improved EEG compared with the AED monotherapy. And in the study of Huang (2020)[45] and Qi(2021)[39], combination treatment with HM and AED significantly improved biomarkers of blood samples such as immunity, inflammation, and nerve growth factor compared with the AED monotherapy.

In all RCTs, HM monotherapy or combination treatment with HM and AED improved TER. In the study of Cao (2016)[40], HM monotherapy or combination treatment with HM and AED significantly improved the seizure frequency, seizure severity, seizure duration, and total symptomatic scores as well as EEG.

7. Evaluation of adverse events

Of the ten studies[36,41,42,45-47,50,51,55,56] that reported adverse events, six[36,45,47,51,55,56] provided a combination therapy of HM and AED, and three[42,46,50] provided HM monotherapy. One study[41] provided HM monotherapy or combination therapy of HM and AED. No adverse events were reported in the HM monotherapy group[42,46,50]. The adverse events observed in the combination therapy group were digestive system disorders (gastrointestinal disorders, nausea, and vomiting), nervous system disorders (memory disturbance and speech disorders), mental system disorders (change of consciousness, drowsiness, and dizziness), lethargy, liver damage, and weight gain. In the AED group, the following adverse events were reported: digestive system disorders (gastrointestinal disorders, nausea, and vomiting), nervous system disorders (dizziness, headache, and memory impairment), mental system disorders (drowsiness), liver damage, and weight increase.

In a meta-analysis of four studies[36,45,47,51] that provided combination treatment (n=246), the HM combination treatment group showed a significantly lower incidence of adverse events than the AED monotherapy group (RR: 0.45, 95% CI: 0.25 to 0.82, p=0.009, I^2=0%). In a meta-analysis of two studies[42,50], the incidence of adverse events was also significantly lower in the HM monotherapy group than in the AED treatment group (RR: 0.08, 95% CI: 0.01 to 0.62, p=0.02, I^2=0%). These results showed that HM combination treatment significantly improved the incidence of adverse events compared with AED monotherapy (Fig. 5).

IV. DISCUSSION

In this study, a total of 23 articles, including one CPG, three SRs, 15 RCTs, and four non-RCTs, were included for final analysis. We summarized the main findings of the clinical guideline, SRs, and main research characteristics of the included 19 clinical studies (RCTs and non-RCTs) and analyzed the types and frequency of HM prescriptions. The quality evaluation results and meta-analysis of the efficacy and safety of the included studies were also reported.

The TCM CPG for pediatric epilepsy included information on treatment, definition, diagnosis, cirrhosis, and prevention of the disease. The guideline recommended HMs and Chinese patent medicines according to the pattern of epilepsy. Other treatment strategies were recommended, including acupuncture, embedding therapy, and moxibustion. The level of recommendation was not high, ranging between C and D. This is the only CPG in the world that uses traditional medicine for the treatment of pediatric epilepsy. The World Health Organization greatly emphasizes the integration of traditional medicine with modern medicine[57]. Therefore, the World Health Organization strategy 2014~2023 has included

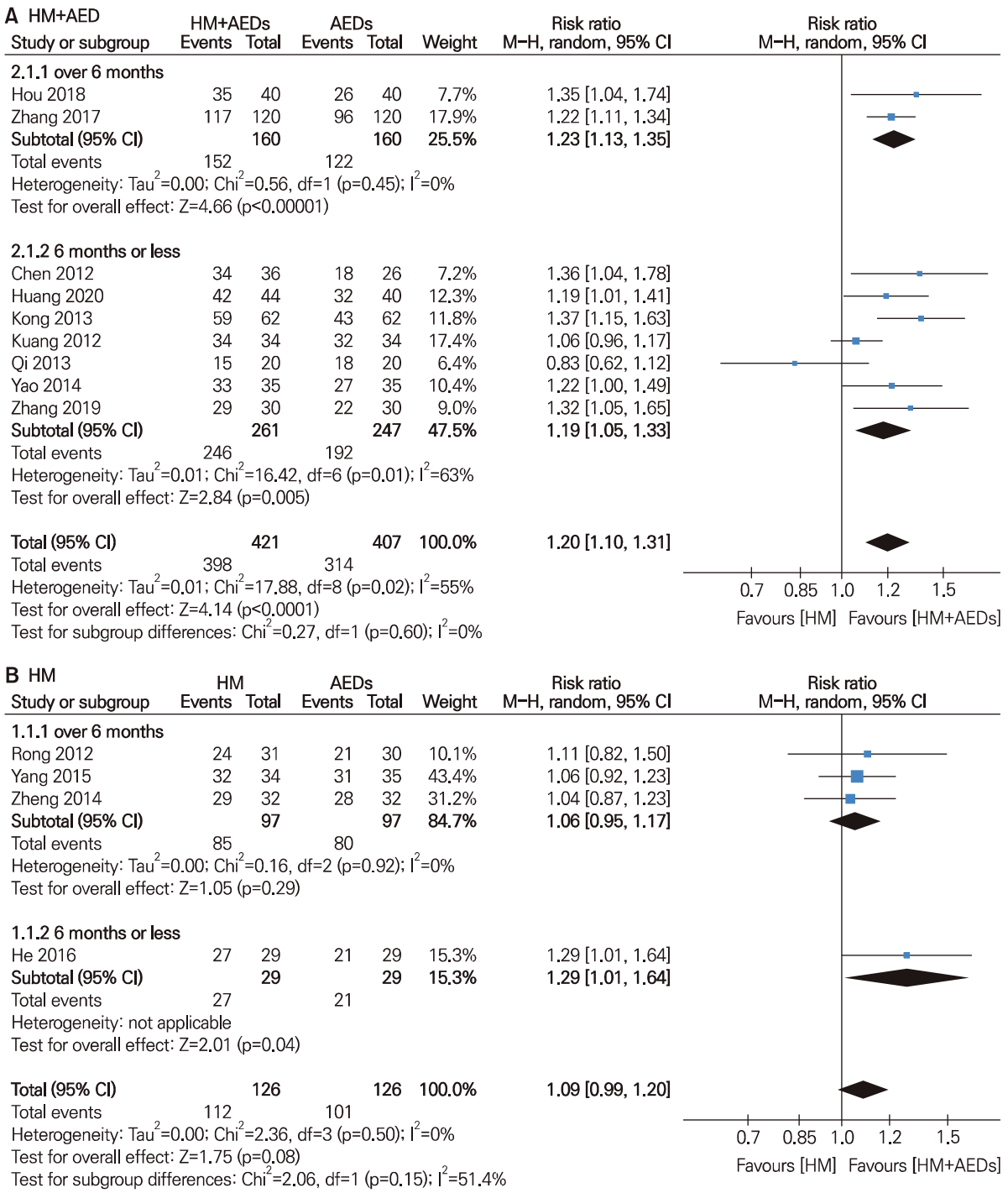

Fig. 4. Forest plots for comparison of TER between herbal medicine and psychotropic drug groups. Sensitivity analysis after (A) combined therapy with HM and AED (B) monotherapy with HM.
AEDs: antiepileptic drugs, HM: herbal medicine, TER: total effective response.

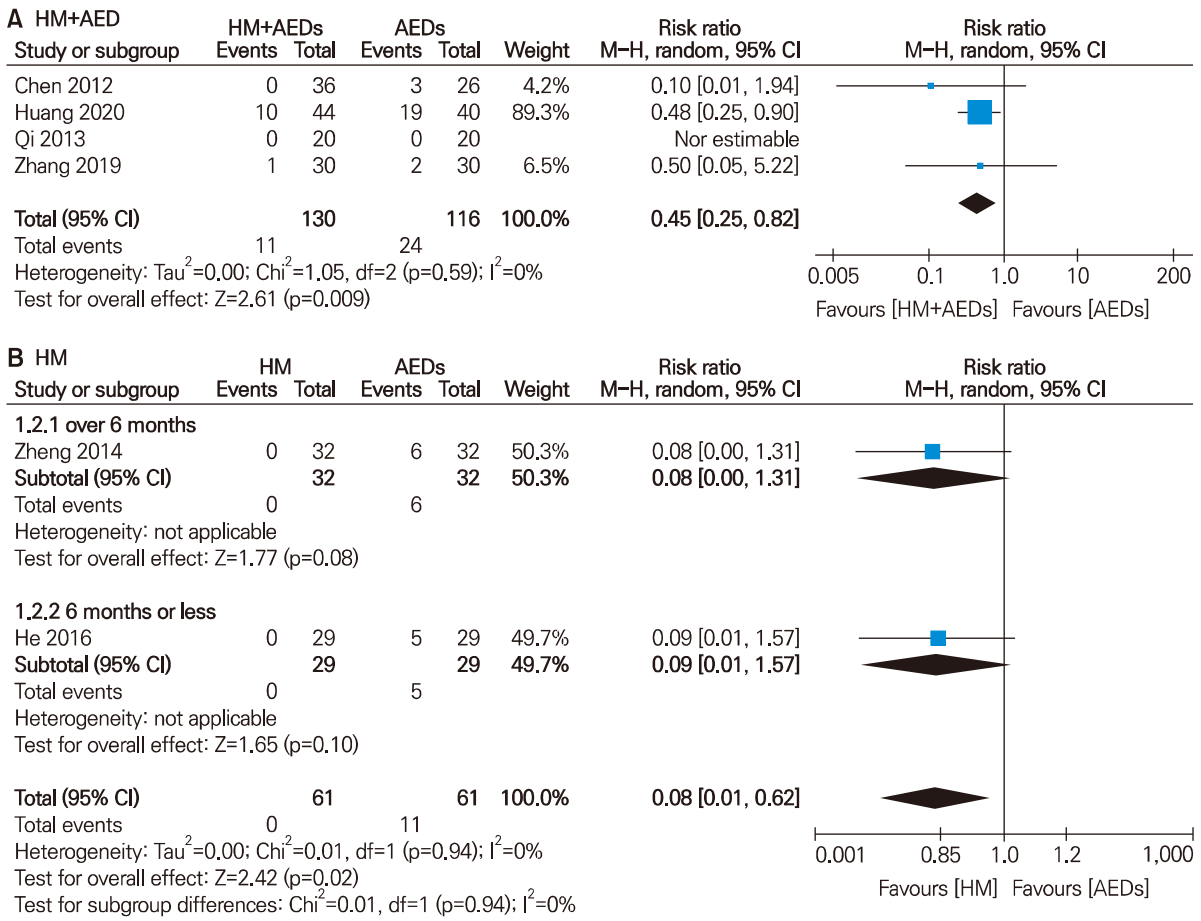

Fig. 5. Forest plots for comparison of TER between herbal medicine and psychotropic drug groups. Sensitivity analysis after (A) combined therapy with HM and AED (B) monotherapy with HM.
AEDs: antiepileptic drugs, HM: herbal medicine, TER: total effective response.

methods for integrating traditional medicine with the national health system, enhancing the efficacy, quality, and safety, and improving the availability and accessibility of traditional medicine for epilepsy management. Epilepsy treatment is clearly related to cultures and societies, and traditional medicine generally considers behavioral, nutritional, psychological, and social factors[20]. Furthermore, a recent patient registration study was conducted in China to review the consistency of treatment by applying the developed guideline for treating 200 patients recruited from 10 hospitals[58]. Therefore, it is necessary to improve the applicability and accessibility of traditional medicine for epilepsy management in the national public health system. This guideline integrated TCM for the management of pediatric epilepsy and may serve as a good model for the development of Korean medicine CPG. However, a comprehensive search of Korean and Japanese databases should be conducted, and the international standard of grading the recommendations and evaluating the evidence levels should be utilized as well[20].

In three SRs, two of these provided quantitative results through meta-analysis. In most evaluation indices, HM monotherapy or combination treatment was effective compared with AED treatment. However, the search date for the latest SR[33] of pediatric epilepsy was 2015. Additionally, a recent study re-

viewed and evaluated SRs of epilepsy in children and adults[59]. In this study, most of the SRs scored 5~8 in the AMSTAR evaluation, which was rated as medium quality, and no studies were rated as high quality. Therefore, in the future, a SR with more rigorous development methodologies and reflective of the latest evidence, including detailed descriptions of the protocols and searches in Korean and Japanese databases, is warranted[59] to provide the evidence of HM for pediatric epilepsy.

Many diagnostic criteria were applied for the diagnosis of pediatric epilepsy. The diagnostic standards used in the studies were those that were set in China or textbooks rather than internationally accepted standards. For a clear selection of participants in clinical studies, consistent use of the internationally accepted Classification of the Epilepsies of International League Against Epilepsy, and a clear description of the used diagnostic criteria are required[11].

The phlegm-retained fluid (Dam-eum) were related to most of pattern identification in five studies. The phlegm and blood stasis, which were considered as the pathological products contributing the pathogenesis of epilepsy[60]. Therefore TCM treatment of eliminating phlegm can inhibits seizures, thereby protecting the nervous system[61]. Pattern identification is a key feature of Korean medicine and TCM that reflects the individual symptoms of the patients and enables personalized treatment[62]. Of the included studies, some studies have performed five kinds of pattern identification, which were recommended in the TCM CPG[31]. In future clinical studies, standardized pattern identification should be applied consistently, and the pattern identification method recommended in clinical guidelines may be used[31,62].

The main evaluation tools used to assess treatment effects were the TER and seizure frequency. Most TER used in the included studies were *Guiding principles for clinical research on new drug of TCM*[63]; however, various TER were used. Thus, future studies should use a standardized scale. An EEG was used as outcome measurement in included many SRs of a recent review[59]. EEG play a major role in diagnosis and management of patients with epilepsy[64]. Therefore, in the further study, many biological evaluation tools, such as EEG, neurotrophic factors, and blood immunity and inflammation levels, are also need to be considered to provide objective evidences and the mechanism regading treatment effect of HM for pediatric epilepsy. In particular, the TCM symptom standard in TCM CPG for pediatric epilepsy, that comprehensively considers consciousness disorder, spasticity, convulsions, and changes on EEG, may be a considered as the main evaluation tools[31].

Various HM prescriptions and dosage forms were used, and several Chinese patent medicines were also observed. Although prescriptions with different effects were used, most prescriptions were Liver-pacifying medicinal (Pyeonggan-yag), Water-draining medicinal (Lisu-yag) and orifice-opening medicinal (Gaegyu-yag) that reflected the existing TCM theories. Liver-pacifying and wind-extinguishing treatment is a representative TCM for epilepsy, and its effects have been demonstrated in many experimental and clinical studies[65]. Orifice-opening medicinal also is used to treat various brain diseases such as stroke, demetia, and epilepsy[61]. In most prescriptions, medicines with multiple therapeutic effects were included.

Analysis of the HM ingredients showed that Gastrodia elata (Cheonma), Poria cocos (Boglyeong), Uncaria sinensis (Jogudeung), and Acorus gramineus (Seogchangpo) were used more than 10 times. In particular, Gastrodia elata (Cheonma) was the most frequently observed ingredient, as used in 14 different HMs. The anticonvulsant effects of Gastrodia elata have been investigated in previous studies. Gastrodia elata is thought to regulate the mitogen-activated protein kinase (MAPK) pathway and gastrodin to sup-

press seizures. In recent studies, Gastrodia elata was shown to regulate the Mammalian target of rapamycin (mTOR) pathway and to improve the loss of neurons in the hippocampus for anticonvulsant effects[66,67]. Poria cocos (Boglyeong) is one of the water-draining and swelling-dispersing medicinal used for various diseases. The triterpene component of Poria cocos acted on gamma-aminobutyric acid (GABA) to exhibit anticonvulsant effects in a mice model of chronic epilepsy[68]. Uncaria sinensis is a medicinal ingredient used for convulsive disorders. Rhynchophylline, an active ingredient contained in Uncaria sinensis, had anticonvulsant effects in animal studies and was shown to act through the MAPK pathway to inhibit sodium release by cell membrane channels and protect hippocampal neurons[67]. Acorus graminneus is also an ingredient commonly used for various diseases. It suppresses hippocampal nerve cell excitation, stimulates nerve cell growth factors, and activates GABA for anticonvulsant effects[67]. Buthus martensii (Jeongal) is a key animal ingredient with anticonvulsant effects and is used for various nervous system and musculoskeletal disorders, such as stroke, headache, and joint pain. Anticonvulsant peptides extracted from scorpions are low-molecular substances that can easily cross the blood-brain barrier to exhibit anticonvulsant effects. These peptides are thought to control seizures by regulating sodium in the cell membrane channels to reduce neuronal excitability[67]. In addition, many herbal ingredients, such as Paeonia lactiflora (Jagyag), Bupleurum falcatum (Shiho), Zizyphus jujuba (Daejo), Pinellia ternata (Banha), Paeonia suffruticosa (Mogdanpi), Sinomenium acutum (Bang-gi), Corydalis Tuber (Hyeonhosaeg), Salvia miltiorrhiza (Dansam), Ganoderma lucidum (Yeongji), Bactryticatus Bombyx (Baeg-gangjam), and Cryptotympana dubia (Seontoe), have anticonvulsant effects[67]. Since HM prescription is composed of the various single HMs mentioned above, it is thought to exert synergistic effects through multiple mechanisms mentioned above.

The included studies provided HM and AED combination therapies more often than HM monotherapy. Most included studies showed that HM combination treatment improved the TER compared with AED monotherapy. Meta-analysis showed that HM combination treatment significantly improved the TER scale score compared with AED monotherapy. These results were consistent with previous SR[33] and also the RR of TER was similar to previous study. In addition, the incidence of adverse events was lower in the HM combination treatment group than in the AED monotherapy group. No adverse events were observed in the HM monotherapy group. In contrast, various adverse events were reported in the combination treatment group. These findings indicated that HM combination treatment may improve the patient's symptoms and side effects compared with AED monotherapy. The long-term use of AEDs may cause many side effects including serious complications[12,13]. Especially, parents using complementary and integrative medicine (CIM) believe that CIM has fewer side effects and is less harmful than conventional pharmacology[69]. The HM, the most usual form of CIM, in developed countries are served for seizure control, reducing adverse events caused by AEDs[18]. And approximately 30% of patients experience drug-resistant epilepsy, and their seizures persist even when combination therapy of two or more drugs is applied[9]. To develop novel medications for refractory patients we should emphasize not only the efficacy but also the safety profile of the intended drug candidates[70]. Therefore, HM may be considered as potential therapy to overcome the limits of AEDs. Furthermore, since HM have multi-targets and mechanisms, HM may have the advantage of not only treating the epilepsy but also improving the overall condition of the patient[71]. However, the risk of se-

lection bias, performance bias, and other biases lowered the quality of the studies, implicating that the included studies might have missed the safety and effects of HM combination treatment. Since to present the recent research trends, only studies conducted in the last 10 years were included, and multiple search engines/databases were not comprehensively searched. Furthermore, the TER evaluation scale was not standardized, and the TER was calculated using different standards in the included studies. A limited number of studies were included, and the number of participants in each study was insufficient. Many studies also have no description of the safety of HMs. Therefore, future studies need to be well-designed with rigorous standards to provide evidence of HM for pediatric epilepsy to use HM in the clinical setting.

Most included studies show combination therapies of HM and AEDs are used. In several experimental studies, active ingredients of various HMs interacted with AEDs and showed enhanced efficacy[16,72]. The complexity and the wide range of HMs lead to difficulties in determining drug interactions. Moreover, only a few studies have evaluated the side effects of combination therapies. In a recent experimental study, a combined administration of Gastrodia elata and carbamazepine enhanced the efficacy of carbamazepine, thereby also increasing the side effects of carbamazepine[73].

Some limitations need to be considered in interpreting this study's findings. First, this study only included TCM studies that were published in the last 10 years. Therefore, a comprehensive SR and meta-analysis study that provides the latest evidence for the efficacy and safety of HMs should be conducted. As the included studies had poor qualities, well-designed large-scale RCTs also should be performed. Second, various epilepsy diagnostic standards were used in the included studies. For a better selection of participants, internationally accepted diagnostic criteria, such as the Classification of the Epilepsies of International League Against Epilepsy, must be used. Third, as various HMs were prescribed, the clinical heterogeneity between the studies was significant. Thus, standardized HM prescriptions suitable for the clinical setting in South Korea need to be used in further clinical trials. Our results of the analysis regarding frequently used HMs for pediatric epilepsy can provide basic data to select standardized HM prescriptions. Epilepsy requires long-term treatment. The mean treatment period among the included studies was at least eight months. Long-term use of HM increases an economic burden with patients. Therefore, to increase the clinical utility of HMs, HM granules covered by health insurance may be a useful alternative. And further clinical studies are needed to expand the indications of previous HM granules covered by health insurance to reducing an economic burden with patients[74]. Banhabaekchulcheonma-tang, Shihogyeji-tang, Eejin-tang, and Gungha-tang may be suitable candidates in South korea[24]. Fourth, there was a lack of evidence on the safety of combined HM and AED. Relevant mechanism studies and prospective registry studies must be conducted to provide the basis for integrating Korean and western medicine[75].

V. CONCLUSION

TCM studies on pediatric epilepsy, published in the last 10 years, were reviewed. A total of 23 articles, including one CPG, three SRs, 15 RCTs, and four non-RCTs, were analyzed. The conclusions were as follows.

1. The TCM CPG for pediatric epilepsy included comprehensive information on the definition, diagnosis, pattern identification, and prevention of epilepsy. The overall level of recommendation was not high,

ranging between C and D.

2. In the selected three SRs, the latest search date was in 2015, and protocols were not registered in every study. In most studies, HM treatment was effective. However, only a few studies reported adverse reactions.

3. The classification of the International League Against Epilepsy was the most commonly used tool for the diagnosis of epilepsy. However, various diagnostic standards were used. Pattern identification was performed in five studies, mainly related to the phlegm-retained fluid (Dam-eum).

4. The main evaluation tool used was the TER. Other evaluation tools, such as seizure frequency, the TCM symptom standards, the TCM symptom scale, cognitive functions, patient compliance, EEG, neurotrophic factors, and immunity and inflammation levels, were also used for evaluation.

5. Combinations of HM and AED were provided more often than HM monotherapy. Pyeonggan medicine, Risuyak, and Gaegyuyak were widely used. Common ingredients were Gastrodia elata, Poria cocos, Uncaria sinensis, and Acorus gramineus.

6. The mean treatment period was about eight months. The most common treatment period was a year.

7. Combination therapies using HM and AEDs significantly improved TER compared with AED monotherapy. The incidence of adverse events was also significantly lower in the combined therapy treatment group than in the AED monotherapy group. However, the overall risk of bias was high, and only the latest studies published in the last 10 years were selected. Therefore, the safety and effects of combination therapies using HM are inconclusive.

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Appendix 1. Details of used Herbal Medicine

First author (year)	Name of herbal medicine	Formula	Herbal medicine ingrediants
RCT			
Chen (2012)	Seongsin-yugan-tang	Decoction	Uncaria sinensis (Jogudeung) 18 g, Haliotis gigantea(Seog-gyeolmyeong) 12 g, Scutellaria baicalensis (Hwang-geum) 12 g, Poria cocos (Boglyeong) 12 g, Gentiana Scabra (Yongdamcho) 12 g, Liriope platyphylla (Maegmundong) 12 g, Gastrodia elata (Cheonma) 12 g, Carthamus tinctorius (Honghwa) 12 g, Salvia miltiorrhiza (Dansam) 12 g, Curcuma wenyujin (Ulgeum) 9 g
Kuang (2012)	NR	NR	Uncaria sinensis (Jogudeung), Buthus martensii (Jeongal), Fritillaria cirrhosa(Chenpaemo), Codonopsis pilosula (Dangsam), Poria cocos (Boglyeong), Liriope platyphylla (Maegmundong)
Ma (2012)	NR	NR	Bos taurus (Woohwang) 1 g, Moschus berezovskii (Sahyang) 1 g, Gastrodia elata(Cheonma) 25 g, Aconitum koreanum (Baegbuja) 25 g, Zingiber officinale (Geongang) 25 g, Cinnamomum cassia (Yug-gye) 25 g, Foeniculum vulgare (Sohoehyang) 25 g, Evodia rutaecarpa (Osuyu) 25 g, Schizonepeta tenuifolia (Hyung-gae) 25 g, Aconitum carmichaeli (Buja) 25 g, Bactryticatus Bombyx(Baeg-gangjam) 25 g, Poria cocos (Boglyeong) 50 g, Atractylodes japonica (Baegchul) 50 g
Rong (2012)	Yongchang capsule Hang-gan capsule	Capsule	Yongchang capsule: Cervus nippon (Nogyong), Acorus gramineus (Seogchangpo), Cuscuta chinensis (Tosaja), Arisaema amurense (Damnamseong), Gastrodia elata (Cheonma), Buthus martensii(Jeongal), Bactryticatus Bombyx (Baeg-gangjam), Pinellia ternata (Banha), Citrus unshiu (Jinpi), Poria cocos (Boglyeong), Dryobalanops aromatica (Yongnoe), Glycyrrhiza uralensis (Gamcho), Hang-gan capsule (not reported constituent herbs)
Kong (2013)	Hwatag-haedog-jogan-tang	Decoction	Hypericum japonicum (Jeongihwang), Rhodiola crenulata (Honggyeongcheon), Gynostemma pentaphyllum (Gyogoram), Pelodiscus sinensis (Byeolgab), Sparganium stoloniferum (Samleung), Polygonum cuspidatum (Hojanggeun), Artemisia capillaris (Injinho), Coptis janponica (Hwanglyeon), Phellodendron amurense (Hwangbaeg)
Qi (2013)	Seongsin-yujeon-tang	Decoction	Scutellaria baicalensis (Hwang-geum) 12 g, Poria cocos (Boglyeong) 12 g, Liriope platyphylla (Maegmundong) 12 g, Gentiana Scabra (Yongdamcho) 12 g, Carthamus tinctorius (Honghwa) 12 g, Gastrodia elata (Cheonma) 12 g, Salvia miltiorrhiza (Dansam) 12 g, Haliotis gigantea (Seog-gyeolmyeong) 15 g, Uncaria sinensis (Jogudeung) 18 g, Tulipa gesneriana (Ulgeumhyang) 9 g
Yao (2014)	Modified Jeong-gan-hwan	Pill	Pteria margaritifera (Jinjumo) 15 g, Gazella subgutturosa (Yeongyang-gag) 15 g, Uncaria sinensis (Jogudeung) 12 g, Buthus martensii (Jeongal) 12 g, Cryptotympana dubia (Seontoe) 15 g, Bactryticatus Bombyx (Baeg-gangjam) 15 g, Bos taurus (Woohwang) 9 g, Aconitum koreanum (Baegbuja) 15 g, Gastrodia elata (Cheonma) 9 g, Poria cocos (Boglyeong) 12 g, Paeonia lactiflora (Baegjagyag) 12 g, Salvia miltiorrhiza (Dansam) 12 g etc.
Zheng (2014)	Modified Cheogdam-tang Modified Jingyeong-hwan Modified Jeong-ganhwan Modified Tong-gyu-hwalhyeol-tang	Decoction , Pill	Those with phlegm epilepsy: Modified Cheogdam-tang Those with fright epilepsy: Modified Jingyeong-hwan Those with wind epilepsy: Modified Jeong-gan-hwan Those with blood stasis epilepsy: Modified Tong-gyu-hwalhyeol-tang
Xue (2015)	Seongsin-yugantang	Decoction	Uncaria sinensis (Jogudeung) 18 g, Haliotis gigantea(Seog-gyeolmyeong) 15 g, Scutellaria baicalensis (Hwang-geum) 12 g, Poria cocos (Boglyeong) 12 g, Gentiana Scabra (Yongdamcho) 12 g, Liriope platyphylla (Maegmundong) 12 g, Gastrodia elata (Cheonma) 12 g, Carthamus tinctorius (Honghwa) 12 g, Salvia miltiorrhiza (Dansam) 12 g, Curcuma wenyujin (Ulgeum) 9 g
Yang (2015)	Ansin-jeong-gantang	Decoction	Scutellaria baicalensis (Hwang-geum),Bupleurum falcatum (Shiho), Curcuma wenyujin (Ulgeum), Cassia tora (Gyeolmyeongja), Uncaria sinensis (Jogudeung), Polygala tenuifolia (Wonji), Phyllostachys bambusoides (Cheonjughwang), Acorus gramineus (Seogchangpo), Alpinia oxyphylla (Igji), Paeonia lactiflora (Baegjagyag), Pteria margaritifera (Jinjumo), Gastrodia elata (Cheonma), Pericaeta communisma (Jilyong), Poncirus trifoliata (Jisil), Phyllostachys nigra (Jug-yeo)

Appendix 1. Continued 1

First author (year)	Name of herbal medicine	Formula	Herbal medicine ingrediants
He (2016)	Cheogdam-jeong-gantang	Decoction	Acorus gramineus (Seogchangpo) 10 g, Pinellia ternata (Banha) 10 g, Uncaria sinensis(Jogudeung) 10 g, Gastrodia elata (Cheonma) 6 g, Platycodon grandiflorum (Gilgyeong) 10 g, Bactryticatus Bombyx(Baeg-gangjam) 10 g, Pericaeta communisma (Jilyong) 10 g, Fritillaria thunbergii (Jeolpaemo) 10 g, Citrus unshiu(Jinpi) 10 g, Polygala tenuifolia (Wonji) 6 g, Paeonia lactiflora (Baegjagyag) 10 g, Glycyrrhiza uralensis (Gamcho) 5 g Those with frequent seizures add Scolopendra subspinipes mutilans (Ogong) 3 g, Buthus martensii (Jeongal) 5 g Those with anorexia or Abdomen distension add Raphanus sativus (Naebogja) 10 g, Massa Medicata Fermentata (Singog) 10 g Those with phlegm-drool congestion add Baijin-wan (consists of Alumen (Baegban), Curcuma wenyujin (Ulgeum), Mentha arvensis (Bagha))
Zhang (2017)	Jeong-gan pill	Granule	Astragalus membranaceus (Hwang-gi) 20 g, Angelica gigas (Dang-gwi) 20 g, Gastrodia elata (Cheonma) 20 g, Fritillaria cirrhosa (Chenpaemo) 20 g, Arisaema amurense (Damnamseong) 20 g, Pinellia ternata (Banha) 20 g, Citrus unshiu (Jinpi) 10 g, Poria cocos (Boglyeong) 10 g, Cnidium officinale (Cheongung) 20 g, Salvia miltiorrhiza (Dansam) 20 g, Panax ginseng (Insam) 20 g, Liriope platyphylla (Maegmundong) 20 g, Acorus gramineus (Seogchangpo) 10 g, Polygala tenuifolia (Wonji) 10 g, Buthus martensii (Jeongal) 6 g, Bactryticatus Bombyx(Baeg-gangjam) 6 g, Glycyrrhiza uralensis (Gamcho) 3 g
Hou (2018)	Hang-gan capsule	Capsule	Acorus gramineus(Seogchangpo) 300 g, Pharbitis nil (Gyeonuja) 300 g, Haliotis gigantea(Seog-gyeolmyeong) 300 g, Magenetitum (Jaseog) 500 g, Buthus martensii (Jeongal) 100 g, Panax notoginseng(Samchil) 200 g, Pericaeta communisma (Jilyong) 300 g, Ossa Draconis (Yong-gol) 500 g, Codonopsis pilosula (Dangsam) 300 g, Uncaria sinensis (Jogudeung) 300 g, Gastrodia elata (Cheonma) 300 g, Scolopendra subspinipes mutilans (Ogong) 100 g, Cryptotympana dubia (Seontoe) 100 g, Fossilia Dentis Mastodi (Yongchi) 500 g, Pinellia ternata (Banha) 200 g, Arisaema amurense (Cheonnamseong) 300 g, Atractylodes japonica (Baegchul) 300 g, Curcuma wenyujin (Ulgeum) 300 g
Zhang (2019)	Modified Yookgunja-tang	Decoction	Rehmannia glutinosa (Sugjihwang), Poria cocos (Boglyeong), Codonopsis pilosula(Dangsam), Angelica gigas (Dang-gwi), Atractylodes japonica (Baegchul), Citrus unshiu (Jinpi), Zizyphus jujuba (Daejo), Pinellia ternata(Banha), Arisaema amurense (Cheonnamseong), Glycyrrhiza uralensis (Gamcho), Polygala tenuifolia (Wonji), Acorus gramineus (Seogchangpo), Zingiber officinale (Saeng-gang)
Huang (2020)	Modified Cheogdam-tang	Decoction	Arisaema amurense (Damnamseong) 4 g, Pinellia ternata (Banha) 3 g, Poncirus trifoliata (Jisil) 6 g, Poria cocos (Boglyeong) 6 g, Citrus reticulata (Gyulhong) 5 g, Acorus gramineus (Seogchangpo) 3 g, Panax ginseng (Insam) 3 g, Phyllostachys nigra (Jug-yeo) 5 g, Glycyrrhiza uralensis (Gamcho) 5 g Those with frequent seizures add Phyllostachys bambusoides (Cheonjughwang) 3 g,Nelumbo nucifera (Yeonjasim) 6 g, Succinum (Hobag) 3 g Those with headache add Chrysanthemum indicum (Gamgug) 6 g, Ilex kudingcha (Gojeongyeob) 6 g Those with stomachache add Paeonia lactiflora (Baegjagyag) 6 g, Corydalis ternata (Hyeonhosaeg) 6 g, Melia toosendan (Cheonlyeonja) 6 g Those with vomiting add Haematitum (Daejaseog) 3 g Those with limb pain add Clematis mandshurica (Wilyeongseon) 6 g, Spatholobus suberectus (Gyehyeoldeung) 6 g
Qi (2021)	Sikgyeong-tang	Decoction	Salvia miltiorrhiza (Dansam) 8 g, Uncaria sinensis (Jogudeung) 5 g, Poria cocos (Bogsin) 5 g, Bactryticatus Bombyx(Baeg-gangjam) 5 g, Phyllostachys bambusoides (Cheonjughwang) 5 g, Atractylodes japonica (Baegchul) 5 g, Curcuma wenyujin (Ulgeum) 5 g, Zizyphus spinosa (Sanjoin) 5 g, Scutellaria baicalensis (Hwang-geum) 5 g, Gastrodia elata (Cheonma) 3 g, Gazella subgutturosa (Yeongyang-gag) 3 g, Pericaeta communisma (Jilyong) 3 g, Acorus Gramineus (Seogchangpo) 3 g, Polygala tenuifolia (Wonji) 3 g, Pteria margaritifera (Jinjumo) 3 g, Bupleurum falcatum (Shiho) 3 g, Cassia tora (Gyeolmyeongja) 3 g, Angelica gigas (Dang-gwi) 3 g, Cnidium officinale (Cheongung) 3 g, Glycyrrhiza uralensis (Gamcho) 4 g, Cryptotympana dubia (Seontoe) 5 pieces

Appendix 1. Continued 2

First author (year)	Name of herbal medicine	Formula	Herbal medicine ingrediants
Non-RCT			
Zou (2012)	Padubunho-hwan	Pill	Croton tiglium (Padu) Basic HM: Acorus gramineus (Seogchangpo) 10 g, Curcuma wenyujin (Ulgeudm) 10 g, Polygala tenuifolia (Wonji), Uncaria sinensis (Jogudeung) 10 g, Pinellia ternata (Banha) 6 g, Citrus reticulata (Gyulhong) 4 g, Poria cocos (Boglyeong) 10 g Those with fright epilepsy add modified Ansin-Jeongji-hwan (consists of Codonopsis pilosula (Dangsam), Poria cocos (Bogsin), Polygala tenuifolia (Wonji), Acorus gramineus (Seogchangpo), Zizyphus spinosa(Sanjoin), Aucklandia lappa (Moghyang), Atractylodes japonica (Baegchul), Glycyrrhiza uralensis (Gamcho)) Those with phlegm epilepsy add modified Cheogdam-tang (consists of Pinellia ternata (Banha), Citrus unshiu (Jinpi), Poria cocos (Boglyeong), Phyllostachys nigra (Jug-yeo), Poncirus trifoliata (Jisil), Arisaema amurense (Damnamseong), Acorus gramineus (Seogchangpo), Codonopsis pilosula (Dangsam), Glycyrrhiza uralensis (Gamcho), Zizyphus jujuba (Daejo), Zingiber officinale (Saeng-gang)) Those with wind epilepsy add modified Jeong-gan-hwan (consists of Gastrodia elata (Cheonma), Fritillaria cirrhosa (Chenpaemo), Arisaema amurense (Damnamseong), Pinellia ternata (Banha), Citrus unshiu (Jinpi), Poria cocos (Boglyeong), Poria cocos (Bogsin), Salvia miltiorrhiza (Dansam), Liriope platyphylla (Maegmundong), Acorus gramineus (Seogchangpo), Bactryticatus Bombyx(Baeg-gangjam), Polygala tenuifolia (Wonji), Succinum (Hobag), Bambusae Sulcus (Juglyeog), Buthus martensii (Jeongal), Zingiber officinale (Saeng-gang), Glycyrrhiza uralensis(Gamcho), Cinnabaris (Jusa)) Those with blood stasis epilepsy add modified Boyang-hwano-tang (consists of Paeonia lactiflora (Jyeogjagyag), Cnidium officinale (Cheongung), Angelica gigas (Dang-gwi), Pericaeta communisma (Jilyong), Astragalus membranaceus (Hwang-gi), Prunus persica (Doin), Carthamus tinctorius (Honghwa))
Cao (2016)	Jeong-gan-sanand HM	Granule or decoction	Jeong-gan-san(consists of Buthus martensii (Jeongal), Scolopendra subspinipes mutilans (Ogong), Cervus nippon (Nog-gag), Bactryticatus Bombyx(Baeg-gangjam), Paeonia lactiflora (Baegjagyag), Arisaema amurense (Damnamseong), Fossilia Dentis Mastodi (Yongchi), Gazella subgutturosa (Yeongyang-gag)) HM: Acorus gramineus (Seogchangpo) 10 g, Curcuma wenyujin (Ulgeum) 10 g, Polygala tenuifolia (Wonji) 10 g, Gastrodia elata (Cheonma) 10 g, Uncaria sinensis (Jogudeung) 10 g, Pinellia ternata (Banha) 6 g, Citrus reticulata (Gyulhong) 4 g, Poria cocos (Boglyeong) 10 g Those with fright epilepsy add Magenetitum (Jaseog) 15 g, Pteria margaritifera (Jinjumo) 15 g, Those with phlegm epilepsy add Phyllostachys bambusoides (Cheonjughwang) 10 g, Trichosanthes kirilowii (Gwalu) 10 g Those with wind epilepsy add Pericaeta communisma (Jilyong) 10 g, Zaocys dhumnades (Ochosa) 10 g Those with blood stasis epilepsy add Panax notoginseng(Samchil) 10 g, Prunus persica (Doin) 6 g
Tan (2018)	Angungwoohwang-hwan	Pill	Bos taurus (Woohwang), Bubalus bubalis (Soowoogag), Moschus berezovskii (Sahyang), Pteria margaritifera (Jinjumo), Cinnabaris (Jusa), Realgar (Woonghwang), Coptis janponica (Hwanglyeon), Scutellaria baicalensis (Hwang-geum), Gardenia jasminoides (Chija), Curcuma wenyujin (Ulgeum), Dryobalanops aromatica (Yongnoe)
Xie (2018)	HM includingCryptotympana dubia (Seontoe)	Decoction	Cryptotympana dubia (Seontoe)10 g, Gastrodia elata (Cheonma) 10 g, Uncaria sinensis (Jogudeung) 5 g, Pinellia ternata (Banha) 5 g, Poria cocos (Boglyeong) 5 g, Acorus gramineus (Seogchangpo) 5 g, Bactryticatus Bombyx(Baeg-gangjam) 5 g, Citrus unshiu (Jinpi) 5 g, Buthus martensii (Jeongal) 5 g, Those with high fever add Gypsum Fibrosum (Seog-go), Forsythia viridissima (Yeongyo), Scutellaria baicalensis (Hwang-geum) Those with constipation add Rheum palmatum (Daehwang), Aloe barbadensis (Nohoe) Those with agitation and anxiety add Coptis janponica (Hwanglyeon), Lophatherum gracile (Damjugyeob) liver-kidney yin deficiency and internal stirring wind add Paeonia lactiflora (Baegjagyag), Chinemys reevesii (Gwipan), Angelica gigas (Dang-gwi), Rehmannia glutinosa (Saengjihwang)

HM: herbal medicine, RCT: randomized controlled trials.

Appendix 2. Frequency of Usage of Single HM in HM Prescriptions

Frequency	Single HM
14	Gastrodia elata (Cheonma)
13	Poria cocos (Boglyeong)
11	Uncaria sinensis (Jogudeung), Acorus gramineus (Seogchangpo)
9	Buthus martensii (Jeongal), Bactryticatus Bombyx(Baeg-gangjam), Pinellia ternata (Banha)
8	Curcuma wenyujin (Ulgeum)
7	Scutellaria baicalensis (Hwang-geum), Salvia miltiorrhiza (Dansam), Arisaema amurense (Cheonnamseong), Glycyrrhiza uralensis (Gamcho), Polygala tenuifolia (Wonji), Paeonia lactiflora (Jagyag)
6	Liriope platyphylla (Maegmundong), Citrus unshiu (Jinpi), Pericaeta communisma (Jilyong)
5	Atractylodes japonica (Baegchul), Pteria margaritifera (Jinjumo), Angelica gigas (Dang-gwi)
4	Haliotis gigantea (Seog-gyeolmyeong), Carthamus tinctorius (Honghwa), Codonopsis pilosula (Dangsam),Cryptotympana dubia (Seontoe), Phyllostachys bambusoides (Cheonjughwang), Fritillaria cirrhosa/Fritillaria thunbergii (Paemo),
3	Gentiana Scabra (Yongdamcho), Bos taurus (Woohwang), Coptis janponica (Hwanglyeon), Gazella subgutturosa (Yeongyang-gag), Scolopendra subspinipes mutilans (Ogong), Cnidium officinale (Cheongung), Poncirus trifoliata (Jisil), Phyllostachys nigra (Jug-yeo)
2	Moschus berezovskii (Sahyang), Aconitum koreanum (Baegbuja), Dryobalanops aromatica (Yongnoe),Astragalus membranaceus (Hwang-gi), Panax ginseng (Insam), Bupleurum falcatum (Shiho), Cassia tora (Gyeolmyeongja), Magenetitum (Jaseog), Panax notoginseng(Samchil), Fossilia Dentis Mastodi (Yongchi), Zizyphus jujuba (Daejo), Citrus reticulata (Gyulhong), Succinum (Hobag), Poria cocos (Bogsin), Zizyphus spinosa (Sanjoin), Cinnabaris (Jusa), Prunus persica (Doin), Zingiber officinale (Saeng-gang), Rehmannia glutinosa (Jihwang)
1	Cinnamomum cassia (Yug-gye), Foeniculum vulgare (Sohoehyang), Evodia rutaecarpa (Osuyu), Schizonepeta tenuifolia (Hyung-gae), Aconitum carmichaeli (Buja), Cervus nippon (Nogyong), Cervi Cornu (Nog-gag), Cuscuta chinensis (Tosaja), Hypericum japonicum (Jeongihwang), Rhodiola crenulata (Honggyeongcheon), Gynostemma pentaphyllum (Gyogoram), Pelodiscus sinensis (Byeolgab), Sparganium stoloniferum (Samleung), Polygonum cuspidatum (Hojanggeun), Artemisia capillaris (Injinho), Phellodendron amurense (Hwangbaeg), Tulipa gesneriana (Ulgeumhyang),Raphanus sativus (Naebogja), Massa Medicata Fermentata (Singog), Alumen (Baegban), Mentha arvensis (Bagha), Alpinia oxyphylla (Igji), Platycodon grandiflorum (Gilgyeong), Pharbitis nil (Gyeonuja), Ossa Draconis (Yong-gol), Nelumbo nucifera (Yeonjasim), Melia toosendan (Cheonlyeonja), Chrysanthemum indicum (Gamgug), Ilex kudingcha (Gojeongyeob), Corydalis ternata (Hyeonhosaeg), Haematitum (Daejaseog),Clematis mandshurica (Wilyeongseon), Spatholobus suberectus (Gyehyeoldeung), Croton tiglium (Padu), Aucklandia lappa (Moghyang), Bambusae Sulcus (Juglyeog), Cervi Cornu (Nog-gag), Trichosanthes kirilowii (Gwalu), Zaocys dhumnades (Ochosa), Bubalus bubalis (Soowoogag), Realgar (Woonghwang), Gardenia jasminoides (Chija), Rheum palmatum (Daehwang), Aloe barbadensis (Nohoe), Gypsum Fibrosum (Seog-go), Forsythia viridissima (Yeongyo), Lophatherum gracile (Damjugyeob), Chinemys reevesii (Gwipan)

HM: herbal medicine.

Appendix 3. The Classifications of Each HM in HM Prescriptions according to the Theory of Traditional Chinese Medicine

Type	Subtype	Single HM
Liver –pacifying medicinal (平肝藥)	Wind-extinguishing medicinal (平肝熄風藥)	Gastrodia elata (Cheonma)$^{++}$, Uncaria sinensis (Jogudeung)$^{++}$, Buthus martensii (Jeongal)$^{+}$, Bactryticatus Bombyx(Baeg-gangjam)$^{+}$, Pericaeta communisma (Jilyong)$^{+}$, Gazella subgutturosa (Yeongyang-gag), Scolopendra subspinipes mutilans (Ogong), Cassia tora (Gyeolmyeongja)
	Subduing yang medicinal (平肝潛陽藥)	Pteria margaritifera (Jinjumo)$^{+}$, Haliotis gigantea (Seog-gyeolmyeong)
Water-draining and swelling-dispersing medicinal (利水退腫藥)		Poria cocos (Boglyeong)$^{++}$
Orifice-opening medicinal (開竅藥)		Acorus gramineus(Seogchangpo)$^{++}$, Moschus berezovskii (Sahyang), Dryobalanops aromatica (Yongnoe)
Phlegm-resolving and cough-suppressing and panting-calming medicinal (化痰止咳平喘藥)	Warming and resolving cold-phlegm medicinal (溫化寒痰藥)	Pinellia ternata (Banha)$^{+}$, Arisaema amurense (Cheonnamseong)$^{+}$, Aconitum koreanum (Baegbuja)
	Clearing and resolving heat-phlegm medicinal (淸化熱痰藥)	Phyllostachys bambusoides (Cheonjughwang), Fritillaria cirrhosa/Fritillaria thunbergii (Paemo),Phyllostachys nigra (Jug-yeo)
Blood-activating and stasis-dispelling medicinal (活血祛瘀藥)		Curcuma wenyujin (Ulgeum)$^{+}$, Salvia miltiorrhiza (Dansam)$^{+}$, Carthamus tinctorius (Honghwa), Codonopsis pilosula (Dangsam), Prunus persica (Doin)
Heat-clearing medicinal (淸熱藥)	Dampness-drying medicinal (淸熱燥濕藥)	Scutellaria baicalensis (Hwang-geum)$^{+}$, Gentiana Scabra (Yongdamcho), Coptis janponica (Hwanglyeon)
	Detoxicating medicinal (淸熱解毒藥)	Bos taurus (Woohwang)
Tonifying and replenishing medicinal (補益藥)	Qi-tonifying medicinal (補氣藥)	Glycyrrhiza uralensis (Gamcho)$^{+}$, Atractylodes japonica (Baegchul)$^{+}$, Astragalus membranaceus (Hwang-gi), Panax ginseng (Insam), Zizyphus jujuba (Daejo)
	Blood-tonifying medicinal (補血藥)	Paeoniae lactiflora (Jagyag)$^{+}$, Angelica gigas (Dang-gwi)$^{+}$, Cnidium officinale (Cheongung)
	Yin-tonifying medicinal (補陰藥)	Liriope platyphylla (Maegmundong)$^{+}$,
Tranquillizing medicinal (安神藥)	Heart-nourishing tranquillizing medicinal (養心安神藥)	Polygala tenuifolia (Wonji)$^{+}$, Poria cocos (Bogsin), Zizyphus spinosa (Sanjoin)
	Settling tranquillizing medicinal (鎭驚安神藥)	Magenetitum (Jaseog), Fossilia Dentis Mastodi (Yongchi), Succinum (Hobag), Cinnabaris (Jusa)
Qi-regulating medicinal (理氣藥)		Citrus unshiu (Jinpi)$^{+}$, Poncirus trifoliata (Jisil), Citrus reticulata (Gyulhong)
Exterior-releasing medicinal (解表藥)	Wind-cold-dispersing medicinal (發散風寒藥)	Zingiber officinale (Saeng-gang)
	Wind-heat dispersing medicinal (發散風熱藥)	Cryptotympana dubia (Seontoe), Bupleurum falcatum (Shiho)
Stasis-resolving hemostatic medicinal (化瘀止血藥)		Panax notoginseng (Samchil)

'$^{++}$'means it has been used in over 9 studies and '$^{+}$' means it has been used in over 4 studies.

Appendix 4. AGREE II Checklist Assessment of the Included CPG

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	■ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ■ Expected benefit(s) or outcome(s) ■ Target(s) (e.g., patient population, society)	1
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	■ Target population ■ Intervention(s) or exposure(s) ■ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	1,2
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	■ Target population, sex and age ■ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	1,2
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	■ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ A description of the member's role in the guideline development group	2
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ■ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ■ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	2
6. TARGET USERS *Report the target (or intended) users of the guideline.*	■ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	2
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	■ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ■ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ■ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	1
8. EVIDENCE SELECTION CRITERIA Report the criteria *used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	■ Target population (patient, public, etc.) characteristics ■ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	1,2
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE Describe the strengths and limitations of the evidence. *Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	■ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ■ Appropriateness/relevance of primary and secondary outcomes considered ■ Consistency of results across studies ■ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ■ Applicability to practice context	3,4

Appendix 4. Continued 1

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	■ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	2
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	NA
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	■ How the guideline development group linked and used the evidence to inform recommendations ■ Link between each recommendation and key evidence (text description and/or reference list) ☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	NA
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	NA
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	■ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ■ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	4
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	■ Description of management options ☐ Population or clinical situation most appropriate to each option	5
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ Specific recommendations grouped together in one section	NA

Appendix 4. Continued 2

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☐ Types of facilitators and barriers that were considered ■ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the guideline development process and/or formation of the recommendations	2 NA
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☐ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals o Solutions linked to barrier analysis (see Item 18) o Tools to capitalize on guideline facilitators (see Item 18) o Outcome of pilot test and lessons learned	NA
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	NA
21. MONITORING/AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	NA
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	NA
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☐ Types of competing interests considered ☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ How the competing interests influenced the guideline process and development of recommendations	NA

AGREE: Advancing the science of practice guidelines, CPG: clinical practice guideline, NA: not applicable.