East Asian Herbal Medicine to Reduce Primary Pain and Adverse Events in Cancer Patients: A Systematic Review and Meta-Analysis With Association Rule Mining to Identify Core Herb Combination

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Objective: Cancer pain is an important factor in cancer management that affects a patient’s quality of life and survival-related outcomes. The aim of this review was to systematically evaluate the efficacy and safety of oral administration of East Asian herbal medicine (EAHM) for primary cancer pain and to explore core herb patterns based on the collected data.

Methods: A comprehensive literature search was conducted in 11 electronic databases, namely, PubMed, Cochrane Library, Cumulative Index to Nursing & Allied Health Literature, EMBASE, Korean Studies Information Service System, Research Information Service System, Oriental Medicine Advanced Searching Integrated System, Korea Citation Index, Chinese National Knowledge Infrastructure Database (CNKI), Wanfang Data, and CiNii for randomized controlled trials from their inception until August 19, 2021. Statistical analysis was performed in R version 4.1.1 and R studio program using the default settings of the meta-package. When heterogeneity in studies was detected, the cause was identified through meta-regression and subgroup analysis. Methodological quality was independently assessed using the revised tool for risk of bias in randomized trials (Rob 2.0).

Results: A total of 38 trials with 3,434 cancer pain patients met the selection criteria. Meta-analysis favored EAHM-combined conventional medicine on response rate (risk ratio: 1.06; 95% CI: 1.04 to 1.09, p < 0.0001), continuous pain intensity (standardized mean difference: −1.74; 95% CI: −2.17 to −1.30, p < 0.0001), duration of pain relief (standardized mean difference: 0.96, 95% CI: 0.69 to 1.22, p < 0.0001), performance status (weighted mean difference: 10.71; 95% CI: 4.89 to 16.53, p = 0.0003), and opioid usage (weighted mean difference: −20.66 mg/day; 95% CI: −30.22 to −11.10, p < 0.0001). No significant difference was observed between EAHM and conventional medicine on response rate and other outcomes. Patients treated with EAHM had...
significantly reduced adverse event (AE) incidence rates. In addition, based on the ingredients of herb data in this meta-analysis, four combinations of herb pairs, which were frequently used together for cancer pain, were derived.

**Conclusion:** EAHM monotherapy can decrease adverse events associated with pain management in cancer patients. Additionally, EAHM-combined conventional medicine therapy may be beneficial for patients with cancer pain in increasing the response rate, relieving pain intensity, improving pain-related performance status, and regulating opioid usage. However, the efficacy and safety of EAHM monotherapy are difficult to conclude due to the lack of methodological quality and quantity of studies. More well-designed, multicenter, double-blind, and placebo-controlled randomized clinical trials are needed in the future. In terms of the core herb combination patterns derived from the present review, four combinations of herb pairs might be promising for cancer pain because they have been often distinctly used for cancer patients in East Asia. Thus, they are considered to be worth a follow-up study to elucidate their actions and effects.

**Systematic Review Registration:** [https://www.crd.york.ac.uk/prospero/, identifier CRD42021265804](https://www.crd.york.ac.uk/prospero/)

**Keywords:** East Asian herbal medicine, cancer pain, complementary and alternative medicine, systematic review, meta-analysis, association rule mining

# 1 INTRODUCTION

Pain is an important factor influencing clinical outcomes in the medical management of cancer. Recent literature on the prevalence of cancer pain reports that pain is observed in more than one-third of the patients, that is, 60% of patients with cancer complain of pain (van den Beuken-van Everdingen et al., 2007; van den Beuken-van Everdingen et al., 2016). Cancer pain should not be overlooked in that it not only affects a patient’s quality of life but also affects the patient’s survival-related prognosis in the case that severe pain is not well-managed (Quinten et al., 2009; Beck et al., 2010; Ciucă and Băban, 2017). Although clinicians’ awareness of cancer pain is gradually improving, it has been reported that about one-third of cancer survivors do not have access to proper management (Greco et al., 2014). In addition to this, a significant number of patients still suffer from pain after completing curative treatment (van den Beuken-van Everdingen et al., 2007). Therefore, preparing a more effective and safer treatment strategy for cancer pain is an urgent task in clinical research above all else.

Currently, the WHO Analgesic Ladder is widely used as a framework for managing cancer pain. According to this recommendation, drugs ranging from over-the-counter analgesics to strong opioids can be administered sequentially as the severity of pain increases (Vargas-Schaffer, 2010). However, a large number of patients complain of severe pain that does not respond to treatment even after receiving opioids (Anderson et al., 2000). Because the etiology of cancer-causing pain is very diverse, it is difficult to consistently predict the effect of individual interventions on major outcomes of patients, such as the intensity of pain and functional status. Meanwhile, concerns of medical consumers about opioid administration due to the continuous increase in accidental prescription opioid overdose or patients’ financial problems are also pointed out as important barriers (Calcaterra et al., 2013; Kwon, 2014).

In this context, studies on various integrative therapies that can be used as therapeutic alternatives or to increase patient compliance with first-line pharmacologic treatment for cancer pain have been actively conducted recently (Deng, 2019). In particular, herbal medicine has been widely used as an intervention to relieve pain caused by various diseases for a long time in East Asian countries such as Korea, Taiwan, Japan, and China (Chen HY. et al., 2014; Lin PH. et al., 2016; Arai et al., 2020; Wang and Meng, 2021). Recently, a number of clinical and experimental studies on various problems caused by cancer have been reported based on the scientific methodological approach for East Asian herbal medicine (EAHM) (Lin et al., 2019; Tsai et al., 2019; Kim et al., 2020). Several systematic reviews have already been reported to explore the relieving effect of cancer pain (Wang S.-j. et al., 2013; Lee et al., 2015, 2019; Wang et al., 2019, 2020). Nevertheless, evidence related to the efficacy of EAHM for cancer pain, in general, is still insufficient. More RCTs have been additionally conducted thanks to the quantitative expansion of EAHM-related scientific research in recent years. Thus, studies that reflect these results need to be continued. On the other hand, previous reviews for EAHM comprehensively dealt with several types of EAHM formulas, including multiple herbal ingredients, unlike reviews on conventional medicine (CM) with a single dose and composition. For this reason, it is difficult to identify which of the much herb-related information reflected in the review is useful for clinicians or drug discovery. In addition, there are various methodological flaws, such as no limitation on the route of EAHM administration, insufficient analysis of adverse events, and a mixture of target diseases.
Therefore, we set the following research objectives to provide meaningful evidence to clinicians by comprehensively reviewing the efficacy and safety of EAHM for cancer pain and to explore useful hypotheses for drug discovery: 1) systematic literature review on the efficacy and safety of overall oral EAHM is conducted, focusing on the improvement of pain intensity and response rate of cancer pain excluding secondary pain caused by anti-cancer treatment; 2) Apriori algorithm-based association rule mining is performed on the herb data collected in this review to discover the core herb pattern.

2 METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement (Page et al., 2021). The protocol of this systematic review was registered in PROSPERO (Registration Number: CRD42021265804, available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021265804). The procedure for this review has also been published in a scientific journal for public reading (Jo and Lee, 2021).

2.1 Search Strategy

Randomized controlled trials (RCTs) that evaluated the efficacy of EAHM for cancer pain were searched in the following 11 electronic databases from their inception until August 19, 2021: four English databases (PubMed, Cochrane Library, Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EMBASE), four Korean databases (Korean Studies Information Service System (KISS), Research Information Service System (RISS), Oriental Medicine Advanced Searching Integrated System (OASIS), and Korea Citation Index (KCI)), two Chinese databases (Chinese National Knowledge Infrastructure Database (CNKI) and Wanfang Data), and one Japanese database (Genki). At the time of preparing the protocol for this review, the search for the Wanfang Data database was not planned. However, in the process of researching the literature, more comprehensive data collection was required; hence, a search target database was added. The following Boolean format was used for the search: (Pain[MeSH] OR Pain*[TIAB] OR analgesia OR analges*[TIAB] OR nocicept* OR neuroapth*) AND (“Cancer pain”[TIAB] OR “Cancer patient”[TIAB] OR “Cancer patients”[TIAB] OR Neoplasms[MeSH] OR Neoplasms*[TI] OR Cancer*[TI] OR Tumor*[MeSH] OR Tumor*[TI] OR Carcinoma[MeSH] OR Carcinoma*[TI] OR Adenocarcinoma[MeSH] OR Adenocarcinoma*[TI] OR adenomatous[TI] OR Lymphoma[MeSH] OR lymphom*[TI] OR lymphedema*[TI] OR Sarcoma[MeSH] OR Sarcoma*[TI] OR “Antineoplastic agents”[MeSH] OR antineoplas*[TI] OR ((adenom*[TI] OR adenopath*[TI]) AND malignant*[TI])) AND (“Plants, Medicinal”[MeSH] OR “Drugs, Chinese Herbal”[MeSH]) OR “Medicine, Chinese Traditional”[MeSH] OR “Medicine, Kampo”[MeSH] OR “Medicine, Korean Traditional”[MeSH] OR “Herbal Medicine”[MeSH] OR “Prescription Drugs”[MeSH] OR “traditional Korean medicine”[TIAB] OR “traditional Chinese medicine”[TIAB] OR “traditional oriental medicine”[TIAB] OR “Kampo medicine”[Title/abstract] OR herb*[TIAB] OR decoction*[TIAB] OR botanic*[TIAB]).

In Korean, Chinese, and Japanese databases, these search terms were appropriately modified to perform a search. Detailed search strategies are explicated in Supplementary Figure S1.

2.2 Study Selection

2.2.1 Type of Studies

Only RCTs evaluating the efficacy and safety of oral administration of EAHM for cancer pain were included. There were no restrictions on language and publication time. Some studies were excluded if they met the following criteria: 1) not RCT or quasi-RCT; 2) inappropriate or no control group; 3) unrelated to cancer pain; 4) animal experiments; 5) case reports or review; 6) not published in scientific peer-reviewed journals, including postgraduate theses or dissertations.

2.2.2 Type of Participants

Trials were considered eligible for inclusion if they were conducted in patients with cancer pain, with no restriction on age, gender, or race. Studies that recruited patients’ secondary cancer-related pain caused by other anticancer therapies like chemotherapy or surgery were excluded since this review focused on primary cancer pain.

2.2.3 Type of Interventions

RCTs that compared EAHM as the active intervention in the treatment group versus placebo or conventional medicine (CM) in the control group were included. RCTs that tested EAHM-combined CM (ECCM) versus CM alone were also considered. All forms of EAHM such as decoction, granule, and capsule for the management of cancer pain were included. There were no restrictions on the dose and duration of treatment for EAHM, but the mode of delivery was limited to oral intake. Studies in which East Asian medical interventions such as acupuncture, massage, or non-drug therapy were only combined in the treatment group were excluded. Studies in which the comparators included other EAHMs were excluded. In addition, studies that could not confirm the composition of individual ingredients and herbs of the utilized EAHM prescription were also excluded.

2.2.4 Type of Outcome Measures

The primary outcome for cancer pain patients was the remission rate for each group measured using the Verbal Rating Scale (VRS), Numerical Rating Scale (NRS), and Visual Analogue Scale (VAS). However, most included studies reported remission rates of complete remission (CR), partial remission (PR), mild remission (MR), and no remission (NR) as CR + PR/ all patients. If the remission rate reported by the individual studies is used as is, there is a concern that an outcome lacking consistency may be reported because there is a difference in the categorization criteria for each study. Therefore, the proportion of patients who had remission in each group was used as the response rate by converting the data of the study in which all detailed category information was reported in this review. In addition, individual continuous pain...
intensity outcomes such as NRS and VAS were also adopted as primary outcomes. Secondary outcomes including duration of pain relief, performance status, and opioid usage were used. In the case of performance status, only outcomes measured by the Karnofsky scale, which is used for cancer patients to access the ability to do ordinary works without impairment, were reflected in the results. Meanwhile, in order to evaluate the safety of the intervention for cancer patients, the incidence of adverse events (AEs) was also included as a secondary endpoint.

2.2.5 Data Extraction
According to the above-mentioned search strategy, the titles and abstracts of potentially eligible studies were independently screened by two investigators (HGJ and JS). Afterward, a full-text review was performed based on the inclusion and exclusion criteria. Subsequently, information on the included studies was extracted independently by two reviewers (HGJ and JS). The following information was collected: title, first author’s name, publication year, sample size, participant age, sex distribution, study design, type of cancer, interventions in the treatment and control groups, treatment duration, outcome measures, reported adverse event, and composition with the dosage of EAHM. Any discrepancy was discussed with the third author (DL).

2.2.6 Methodological Quality Assessment
The methodological quality of each included study was evaluated independently by two investigators (HGJ and JS) according to the revised tool for risk of bias in randomized trials, Rob 2.0 (Sterne et al., 2019). It is comprised of five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, and bias in the selection of the reported results. Methodological quality was assessed on three levels: “high risk of bias,” “low risk of bias,” and “some concerns.” Disagreements between the two investigators were resolved with the help of the third author (DL).

2.2.7 Statistical Analysis
2.2.7.1 Evidence Synthesis
Evidence synthesis of the included studies with available data was performed by calculating the effect size and 95% CI using only the random-effects model. Heterogeneity was considered statistically significant when the p-value based on the χ² test was less than 0.10 or I² was 50% or more. Two-sided p < 0.05 was considered statistically significant. Statistical synthesis of individual research results was performed in R version 4.1.1 and R studio program (Version 1.4.1106, Integrated Development for R. RStudio, PBC, Boston, MA) using the default settings of the meta-package (Lortie and Filazzola, 2020). In this review, in order to effectively reveal the exact value of the effect size without relying only on the p < 0.05 significance threshold in the interpretation of the primary outcome synthesis result, a drapery plot was additionally illustrated along with the forest plot (Rückert and Schwarz, 2021). The studies were grouped according to the type of intervention, such as East Asian herbal medicine (EAHM) and East Asian herbal medicine combined conventional medicine (ECCM), and comparator, such as conventional medicine (CM). Summary relative risk (RR) and 95% confidence interval (CI) were calculated for the response rate. Standardized mean difference (SMD) and 95% CIs were calculated for continuous pain intensity and duration of pain relief. Mean difference (MD) and 95% CIs were calculated for opioid usage and performance status. AEs were calculated using the odds ratio because the probability of occurrence of an event is significantly lower than that of other outcomes, and it is necessary to estimate a causal relationship. In order to distinguish publication bias, a contour-enhanced funnel plot was used for the outcome that included the most studies (Peters et al., 2008). For the asymmetry on the visually confirmed funnel plot, Egger’s test (Egger et al., 1997) and Begg’s test (Begg and Mazumdar, 1994) were additionally performed to specifically confirm the existence of publication bias.

2.2.7.2 Association Rule Mining
By analyzing the constituent herb data of EAHM collected from the included study, the potential association rules of core herb combinations were explored. Before proceeding with this analysis, preliminary information for data mining was extracted by first analyzing the frequency of individual herbs. The R studio program (Version 1.4.1106, Integrated Development for R. RStudio, PBC, Boston, MA) was used for the Apriori association rule analysis and plot production. A data fit was done using the “arules” package in R studio (Hahsler et al., 2005). The function of the R package “arulesViz” was applied to generate graphical presentations according to the results (Hahsler, 2017). Mining of frequent hub itemsets and association rules was performed according to the Apriori algorithm method for discovering meaningful relationships between variables in a large database (Agrawal et al., 1993). Through this, it is possible to identify the elements composing the data and the relationship between the elements, and it is being used in various types of medical research aimed at predicting the characteristics of interventions (Leem et al., 2018; Hsieh et al., 2020; Lin et al., 2021).

In the Apriori algorithm, support, confidence, and lift are the main metrics for measuring association. A rule is defined as an expression X → Y, where X, Y ⊆ I and X∩Y = ∅. The herb X and herb Y are called antecedent (left-hand side, LHS) and consequent (right-hand side, RHS) of the rules. Association rules are rules that surpass researcher-specified minimum support and minimum confidence thresholds. The support, supp (X), of an itemset X is a measure of importance defined as the proportion of transactions in the dataset which contain the itemset. The confidence of a rule is defined as conf (X → Y) = supp (XUY)/supp (X), measuring the likelihood of seeing herb Y in a transaction containing herb X. An association rule X → Y needs to satisfy supp (XUY) ≥ σ and conf (X → Y) ≥ δ, where σ and δ are the minimum support and minimum confidence, respectively. Confidence can be interpreted as an estimate of the probability P(Y|X), which is the probability of finding the RHS of the rule in transactions, given that these transactions also contain the LHS. Lift of a rule is defined as lift (X → Y) = (supp (XUY)/supp (X)). Support is the measure to evaluate the usefulness of the association rule and is the proportion of prescriptions containing a specific herb combination pattern in the total
EAHM prescription. When the confidence is close to 1, herb A and herb B are irrelevant because they are close to independence in probability. Meanwhile, if the lift value is large, the relationship between herb A and herb B is interpreted as a strong correlation. In this study, the association rules were identified based on the minimum values for support and confidence being 20 and 80%, respectively. Among them, the core herb combination patterns showing the most distinct association and its constituent herbs were searched.

### 2.2.8 Quality of Evidence According to Outcome Measurements

The overall quality of evidence for each outcome was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) pro (Guyatt et al., 2008). The GRADE assessment evaluates the overall quality of evidence in four levels: very low, low, moderate, and high. The level of evidence is lowered according to certain factors, such as the risk of bias, inconsistency, indirectness, imprecision, and publication bias, respectively.

### 3 RESULTS

#### 3.1 Study Identification

Based on search strategy, a total of 17,247 potentially relevant articles were identified by electronic search in the 11 databases. After the removal of 479 duplicates, 16,768 reports were retrieved. After screening for titles and abstracts, 16,675 articles that met at least one of the exclusion criteria were removed. A full-text assessment was performed on the remaining 78 studies, and 40 articles were excluded for the reasons listed in Figure 1. The bibliographic information of documents excluded after the full-text review is presented in Supplementary Figure S2. Finally, a total of 38 eligible studies were included in this meta-analysis (Lin et al., 2001; Zhang, 2001; Li et al., 2002; Ma et al., 2003; Chen, 2004; Chen et al., 2005; Wu et al., 2005; Cao and Xu, 2006; Zhang et al., 2006; Chen, 2009; Hao, 2009; Zhai et al., 2009; Zhang, 2009; Zhang et al., 2009; Cai, 2010; Li et al., 2010; Fu, 2011; Wang et al., 2011; Zhou, 2011; Cheng et al., 2012; He, 2012; Meng, 2012; Jiang et al., 2013; Wang and Chen, 2013; Chen H. et al., 2014; Liu and Zhou, 2014; Wan et al., 2014; Song et al., 2015; Li et al., 2017a; Li et al.,
| First author (Year) | Type of cancer | Trial design | Number of participants (male/female); age (mean ± SD) | Interventions | Outcome index (intergroup differences p-value) | Course of treatment | Adverse event (case/symptom) |
|---------------------|----------------|--------------|-----------------------------------------------------|---------------|-----------------------------------------------|-------------------|-----------------------------|
| Lin et al. (2001)   | Mixed (including esophageal cancer, gastric cancer, lung cancer, liver cancer, breast cancer, rectal cancer) | RCT | 30 (19/11); 57.23 ± 14.62 years; 30 (18/12); 55.81 ± 15.74 years | 1) Jianwei niantong capsules (4 c, p.o., q.i.d.) 2) WHO 3-step analgesic ladder treatment: aspirin tablets (0.5 g, p.o., q.i.d.); tramadol capsules (50 mg, p.o., q.i.d.); meperidine tablets (50 mg, p.o., q.i.d.) | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.01) | 10 h | E: 18 cases (7 nausea, 6 dizziness, 3 constipation, 2 mild diarrhea) C: 45 cases (13 nausea, 8 vomiting, 6 dizziness, 18 constipation) |
| Zhang (2001)       | Mixed (including gastric, liver, colon, lung, breast cancers) | RCT | 82 (NR gender info); mean 62.4 years (both groups) | 1) Compound strychnos capsule (1 c, p.o., t.i.d.) 1) Indomethacin suppositories (50 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) | 3 weeks | E: 5 cases (due to overdosage, 1 muscle stiffness, 4 dysesthesia of mouth) C: 10 cases (3 hepatic and renal dysfunction, 7 nausea with anorexia) |
| Li et al. (2002)    | Mixed (including lung, gastric, gallbladder, colon, pancreatic, bladder, renal, ovarian, prostate cancers) | RCT | 46 (20/24; both groups); range 51 years, range 25–64 years | 1) Tibetan medicine duywei (3 c, 0.3 mg/c, p.o., t.i.d.) 1) Indomethacin (50 mg, p.o., t.i.d.) 1) Response rate (p < 0.05) | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.05) 3) Pain intensity (p < 0.05) 4) Performance status (p < 0.05) | 3 days | E: 2 cases (2 nausea with stomach discomfort) C: 16 cases (14 gastrointestinal reactions, 2 dizziness with headache) |
| Mo et al. (2003)    | Gastric cancer | RCT | 31 (25/6); 53.1 years, range 28–79 | 1) Jiaojiebaoci tablets (9 g, p.o., t.i.d.) 1) Propoxyphene compound tablets (1 t, p.o., b.i.d.) | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.05) | 15 days | NR |
| Chen (2004)         | Mixed (including liver, gastric, esophageal, pancreatic, colon, metastatic cancers) | RCT | 73 in both groups (46/27); 51 years, range 13–62 years | 1) Shitong decoction 2) WHO 3-step analgesic ladder treatment: morphine sulfate controlled-release tablets (30–60 mg, p.o., b.i.d.); aspirin 0.6 g or indomethacin 25 mg (p.o., t.i.d.) | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.05) 3) Pain intensity (p < 0.05) 4) Performance status (p < 0.05) | 1 week | NR |
| Chen et al. (2005)  | Mixed (including lung, esophageal, gastric, colon, liver, pancreatic cancers) | RCT | 25 (16/9); 54.80 ± 11.35 years | 1) Zhitong capsules (4 c, p.o., t.i.d.) 2) tramadol capsules; morphine sulfate | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.05) | 3 days | E: 12 cases (3 constipation, 2 dizziness, 5 nausea, 2 drowsiness) C: 28 cases (3 stomach discomfort, 11 constipation, 4 dizziness, 7 nausea, 5 drowsiness) |
| Wu et al. (2005)    | Mixed (including esophageal, gastric, colon, liver, pancreatic, other type cancers) | RCT | 30 (17/13); 58.23 ± 7.32 years | 1) Aitongping compound tablets (1 t, p.o., b.i.d.) 1) Compound ciclofenac sodium and Codein tablets (40 mg, p.o., t.i.d.) | 1) Response rate (p < 0.05) 2) Performance status (p < 0.05) | 1 week | E: 0 case C: 3 cases (1 nausea, 1 vomiting, 1 constipation) |
| Cao and Xu (2006)   | Bone metastasis (including lung, prostate, breast, esophageal, nasopharyngeal, thyroid primary cancers) | RCT | 41 (26/15); 59.82 years | 1) Zhiyang zhitong san decoction (200 ml, p.o., b.i.d.) 1) WHO 3-step analgesic ladder treatment: aspirin tablets (0.3 g, p.o., q.i.d.); tramadol capsules (50 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.01) | 10 h | E: 28 cases (8 nausea, 7 vomiting, 6 dizziness, 7 constipation) C: 46 cases (13 nausea, 8 vomiting, 7 dizziness, 18 constipation) |

(Continued on following page)
| First author (Year) | Type of cancer (specific cancer type) | Trial design | Number of participants (male/ female); age (mean ± SD) | Interventions | Outcome index (intergroup differences p-value) | Course of treatment | Adverse event (case/symptom) |
|---------------------|--------------------------------------|--------------|--------------------------------------------------------|---------------|-----------------------------------------------|-------------------|-----------------------------|
| Zhang et al. (2006) | Mixed (including lung, gastric, liver, esophageal, colon cancers) | RCT          | 41 (28/13); 56.2 ± 8.4 years                           | Capsules (50 mg, p.o., q.i.d.), meperidine tablets (50 mg, p.o., q.i.d.) | 1) EAHM formula for individual research (100 ml, p.o., b.i.d.) | 1) Response rate (p < 0.05) | 2 weeks | E: 2 cases (1 nausea and vomiting, 1 constipation); C: 4 cases (1 burning sensation of dorsal region, 3 nausea and vomiting) |
| Chen (2009)         | Bone metastasis (no specific types of primary cancer reported) | RCT          | 35 (19/16); median 52 years, range 39-65 years         | 1) Jiewei Shentong Zhuyu decoction (100 ml, p.o., b.i.d.) | 1) Zoledronic acid with normal saline (4 mg, i.v., at least 2 times in 4 weeks) | 1) Response rate (p > 0.05) | 8 weeks | E: 13 cases (8 fever, 4 nausea and vomiting, 1 myalgia); C: 21 cases (10 fever, 6 nausea and vomiting, 5 myalgia) |
| Hao (2009)          | Bone metastasis (including lung, prostate, breast, esophageal, nasopharyngeal, thyroid primary cancers) | RCT          | 29 (13/16); NR                                         | 1) EAHM formula for individual research (150 ml, p.o., b.i.d.) | 1) Zoledronic acid with 0.9% sodium chloride or 5% glucose 100 ml (4 mg, i.v., once every 3 weeks) | 1) Response rate (p < 0.05) | 30 days | NR |
| Zhai et al. (2009)  | Mixed (including lung, liver, gastric, pancreatic, cervical, ovarian, rectal, colon, other type cancers) | RCT          | 89 (51/38); 56.92 ± 81 years                           | 1) Anti-cancer zheling decoction (150 ml, p.o., b.i.d.) | 1) Bucinaxine tablets (60 mg, p.o., t.i.d.) | 1) Response rate (p < 0.05) | 2 weeks | E: 2 cases (1 nausea, 1 stomach discomfort); C: 12 cases (5 nausea, 2 vomiting, 3 stomach discomfort, 1 excitation, 1 fatigue) |
| Zhang (2009)        | Liver cancer                        | RCT          | 80 (42/38); range 31-68 years                          | Tiaj powder (12 g, p.o., t.i.d.) | 1) WHO 3-step analgesic ladder treatment: Tramadol capsules (50 mg, p.o., t.i.d.); Morphine sulfate tablets (10 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) | 2 weeks | E: 2 cases (No details reported); C: 14 cases (No details reported) |
| Zhang (2009)        | Mixed (specific cancer type NR)     | RCT          | 40 (29/11); 59 years, range 50-79 years               | 1) Wenlan decoction (100 ml, p.o., b.i.d.) | 1) Zoledronic acid with normal saline 50 ml (4 mg, i.v., q.1.m.) | 1) Response rate (p < 0.05) | 1 week | E: 2 cases (2 nausea and vomiting); C: 8 cases (8 nausea and vomiting) |
| Cai (2010)          | Bone metastasis (including prostate, breast, lung, liver, renal, thyroid, colon, nasopharyngeal primary cancers) | RCT          | 40 (NR gender info); 52.1 y, range 42-70 years (both groups) | Yanghe decoction (p.o.) | 2) Zoledronic acid with normal saline 50 ml (4 mg, i.v., q.1.m.) | 1) Response rate (p < 0.05) | 4 weeks | NR |
| Li et al. (2010)    | Esophageal cancer                   | RCT          | 20 (15/5); 58.90 ± 10.17 years                        | 1) Taohongsi decoction (p.o.) | 2) Ondanetron with normal saline 10 ml (8 mg, i.v., 15 min before each chemotherapy) | 1) Response rate (p < 0.05) | 8 days | NR |
| Fu (2011)           | Mixed (including lung, colon, gastric, liver, breast cancers, cholangioma) | RCT          | 64 (43/21); median 55 years, range 45-70 years (both groups) | 1) Gigongtou decoction (p.o., b.i.d.) | 1) Fentanyl transdermal patches (4.2 mg, t.d., q.72.h.) | 1) Response rate (p < 0.05) | 15 days | E: 7 cases (2 constipation, 2 nausea and vomiting, 1 dizziness, 2 drowsiness); C: 31 cases (9 constipation, 10 nausea and vomiting) |

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### TABLE 1 | (Continued) Characteristics of included studies.

| First author (Year) | Type of cancer (including lung, prostate, breast, esophageal primary cancers) | Trial design | Number of participants (male/female); age (mean ± SD) | Interventions | Outcome index (intergroup differences p-value) | Course of treatment | Adverse event (case/symptom) |
|---------------------|-----------------------------------------------------------------------------|--------------|-----------------------------------------------------|---------------|-----------------------------------------------|---------------------|-----------------------------|
| Wang et al. (2011)  | Bone metastasis (including lung, prostate, breast, esophageal primary cancers) | RCT          | 35 (19/16); 55.7 years                              | Trial         | 1) EAHM formula for individual research (200 ml, p.o., b.i.d.) | 35 (17/16); 56.2 years | 1) Response rate (p < 0.01) | 30 days                       |
|                     |                                                                             |              |                                                     | Control       | 1) Panidronate disodium with normal saline 500 ml (60 mg, i.v., q.d.) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.01) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.01) |                     |                             |                             |
| Zhou (2011)         | Liver cancer                                                                | RCT          | 160 (109/51); range 31–68 years (both groups)      | Trial         | 1) Modified Tuqiu powder (12 g, p.o., t.i.d.) | 160 (109/51); range 31–68 years (both groups) | 1) Response rate (p < 0.05) | 1 week                        |
|                     |                                                                             |              |                                                     | Control       | 1) WHO 3-step analgesic ladder treatment:tramadol capsules (50 mg, p.o., t.i.d.); morphine sulfate controlled-release tablets (10 mg, p.o., b.i.d) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
| Cheng et al. (2012) | Bone metastasis (including breast, primary cancer)                          | RCT          | 15 (NR gender info); 42.00 ± 12.32 years, range 27–58 years (both groups) | Trial         | 1) Baihu fuzi decoction (200 ml, p.o., b.i.d.) | 15 (NR gender info); 42.00 ± 12.32 years, range 27–58 years (both groups) | 1) Response rate (p < 0.01) | 16 weeks                      |
|                     |                                                                             |              |                                                     | Control       | 1) Zoledronic acid with 5% glucose 250 ml (4 mg, i.v., q.1.m.) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
| He (2012)           | Bone metastasis (including lung, breast, gastrointestinal, liver, prostate, cervical primary cancers) | RCT          | 28 (18/10); range 46–76 years (both groups)        | Trial         | 1) EAHM formula for individual research (p.o.) 2) Zoledronic acid with normal saline 1000 ml (4 mg, i.v., q.1.m.) | 28 (20/9); range 47–70 years (both groups) | 1) Response rate (p < 0.01) | 8 weeks                       |
|                     |                                                                             |              |                                                     | Control       | 1) Zoledronic acid with normal saline 1000 ml (4 mg, i.v., q.1.m.) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
| Meng (2012)         | Bone metastasis (including lung primary cancer)                             | RCT          | 21 (10/11); range 41–64 years (both groups)        | Trial         | 1) EAHM formula for individual research (150 ml, p.o., b.i.d.) | 21 (11/10); range 41–64 years (both groups) | 1) Response rate (p-value NR) | 2 weeks                       |
|                     |                                                                             |              |                                                     | Control       | 1) Zoledronic acid with normal saline 100 ml (4 mg, i.v., q.1.w.) |                     | 2) Pain intensity (p-value NR) |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
| Jiang et al. (2013) | Colorectal cancer                                                           | RCT          | 32 (18/14); range 12.4 years (both groups)         | Trial         | 1) EAHM formula for individual research (200 ml, p.o., b.i.d.) | 31 (18/13); range 12.8 years (both groups) | 1) Response rate (p-value NR) | 8 weeks                       |
|                     |                                                                             |              |                                                     | Control       | 1) Oxaplatin with 5% glucose (135 mg, i.v., q.2.w.) |                     | 2) Pain intensity (p-value NR) |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
| Wang & J. et al. (2013) | Mixed (including lung, liver, gastric, pancreatic, esophageal, breast cancers) | RCT          | 40 (25/14); 41.2 ± 9.7 years (both groups)         | Trial         | 1) Gexia zhuyu decoction combined Shixiao powder 2) WHO 3-step analgesic ladder treatment: non-opioids (aspirin); weak opioids (codeine); strong opioids (morphine) | 40 (29/11); 41.8 ± 8.6 years (both groups) | 1) WHO 3-step analgesic ladder treatment: non-opioids (aspirin); weak opioids (codeine); strong opioids (morphine) | 90 days                       |
|                     |                                                                             |              |                                                     | Control       | 1) Morphine sulfate sustained-release tablets (10-30 mg, p.o., b.i.d.) |                     | 1) Response rate (p < 0.025) |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |
| Chen H. et al. (2014) | Mixed (including lung, liver, gastric, colon cancers)                       | RCT          | 50 (26/24); 62 ± 13 years (both groups)             | Trial         | 1) Xiuju decoction (250 ml, p.o., b.i.d.) 2) Morphine sulfate sustained-release | 50 (26/22); 59 ± 15 years (both groups) | 1) Response rate (p < 0.05) | 24 weeks                      |
|                     |                                                                             |              |                                                     | Control       | 1) Morphine sulfate sustained-release tablets (10-30 mg, p.o., b.i.d.) |                     | 1) Response rate (p < 0.05) |                             |
|                     |                                                                             |              |                                                     |               | 1) Response rate (p < 0.05) |                     |                             |                             |

(Continued on following page)
### TABLE 1 | (Continued) Characteristics of included studies.

| First author (Year) | Type of cancer (including lung, breast, prostate, cervical, gastric, other type primary cancers) | Trial design | Number of participants (male/female); age (mean ± SD) | Interventions | Outcome index (intergroup differences p-value) | Course of treatment | Adverse event (case/symptom) |
|---------------------|-------------------------------------------------------------------------------------------------|--------------|-----------------------------------------------------|---------------|-----------------------------------------------|---------------------|-----------------------------|
| Liu and Zhou (2014) | Gastric cancer                                                                                  | RCT          | 31 (23/8); 63.45 ± 11.51 years                      | Tablets (10–30 mg, p.o., b.i.d.) | 1) Buqi Huoxue decoction (p.o.) 2) Pantoprazole with normal saline 100 ml (40 mg, i.v., q.d.) 3) Granisetron with 5% glucose 50 ml (3 mg, i.v., q.d.) 4) Oxaliplatin with 5% glucose 500 ml (20 mg, i.v., q.d.) 5) Tegafur with 5% glucose 500 ml (0.8 g, i.v., q.d.) 6) Calcium folinate with 5% glucose 250 ml (200 mg, i.v., q.d.) | 1) Recurrence rate (p < 0.01) 2) Other analgesics usage (p < 0.05) | 12 weeks NR |
| Song et al. (2015)  | Mixed (including liver, abdominal and retroperitoneal lymph node, bone metastasis, lung, pelvic metastatic cancers) | RCT          | 38 (19/19); 53 ± 6.2 years 34 (17/17); 56.3 ± 2.0 years | 1) Compound Sangsh mixture (p.o., b.i.d.) 2) Morphine sulfate sustained-release tablets (30 mg, p.o., b.i.d.) | 1) Morphin sulfate sustained-release tablets (30 mg, p.o., b.i.d.) | 1) Response rate (p-value NR) | 30 days E: 7 cases (3 gastrointestinal reactions including nausea and vomiting, 4 constipation) C: 7 cases (10 gastrointestinal reactions including nausea and vomiting, 2 constipation, 2 urinary retention, 1 central nervous system toxicity) E: 4 cases (2 constipation, 1 pruritus, 1 drowsiness) C: 14 cases (4 constipation, 3 pruritus, 1 urinary retention, 5 drowsiness, 1 dyspnea) | 7 days |
| Chen et al. (2017)  | Bone metastasis (including lung, breast, prostate, ovarian, gastric, renal primary cancers)      | RCT          | 16 (9/7); range 38-77 years 16 (11/5); range 43-78 years | 1) Hogu Xioaji prescription (p.o., q.d.) 2) Zoledronic acid with normal saline 250 ml (4 mg, i.v., q.1.w.) | 1) Response rate (p > 0.05) 2) Performance status (p > 0.05) | 60 days NR |
| Li et al. (2017a)   | Mixed (including lung, gastric, colon, esophageal, liver, breast cancers)                        | RCT          | 90 (50/40); 57.86 ± 16.45 years 90 (48/42); 58.36 ± 15.96 years | 1) Xuexi Zhuyu decoction (150 ml, p.o., b.i.d.) 2) Oxycodone hydrochloride sustained-release tablets (10–120 mg, p.o., b.i.d.) | 1) Oxycodone hydrochloride sustained-release tablets (10–120 mg, p.o., b.i.d.) | 1) Response rate (p > 0.05) 2) Pain intensity (p < 0.05) 3) Performance status (p < 0.05) 4) Opioid usage (p < 0.05) | 4 week E: 104 cases (38 constipation, 20 nausea, 18 vomiting, 12 dizziness, 16 anorexia) C: 194 cases (58 constipation, 38 nausea, 30 vomiting, 32 dizziness, 36 anorexia) Both groups of patients experienced adverse events such as constipation, (Continued on following page) |
| Li et al. (2017b)   | Mixed (including lung, gastric, colon, esophageal, liver, breast cancers)                        | RCT          | 60 (38/22); 51.14 ± 18.42 years 60 (39/21); 50.88 ± 18.42 years | 1) Genis Zhuyu decoction (150 ml, p.o., b.i.d.) 2) Oxycodone | 1) Oxycodone hydrochloride sustained-release tablets (10–120 mg, p.o., b.i.d.) | 1) Response rate (p > 0.05) 2) Pain intensity (p < 0.05) | 4 weeks Both groups of patients experienced adverse events such as constipation, (Continued on following page) |
| First author (Year) | Type of cancer | Trial design | Number of participants (male/female); age (mean ± SD) | Interventions | Outcome index (intergroup differences p-value) | Course of treatment | Adverse event (case/symptom) |
|---------------------|----------------|--------------|------------------------------------------------------|---------------|-------------------------------------------|-------------------|----------------------------|
| **Jo et al. (2018)** | Mixed (including lung, gastric, colon, liver, breast cancers) | RCT | 26 (13/13); 57.54 ± 7.11 years | | | | |
| | | | 26 (12/14); 56.87 ± 4.54 years | 1) Xuelu Zhuyu decoction (200 ml, p.o., b.i.d.) | 3) Performance status (p < 0.05) | 30 days | nausea, vomiting, dizziness, anorexia, and dysuria. Detailed information NR. |
| **Quan et al. (2020)** | Mixed (including lung, liver, breast cancers) | RCT | 120 (65/55); 53.24 ± 16.10 years | 1) Morphine sulfate controlled-release tablets (10-30 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) | 30 days | |
| **Liu Yang (2018)** | Mixed (including lung, liver, breast cancers) | RCT | 23 (13/10); 61.35 ± 9.89 years | 1) Cinnobufotalin capsules (0.5 g, p.o., t.i.d.) 2) Morphine sulfate sustained-release tablets (10 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) 2) Pain intensity (p < 0.01) 3) Performance status (p < 0.01) | 4 weeks | E: 23 cases (9 constipation, 4 vomiting) C: 44 cases (16 anorexia, 17 constipation, 11 vomiting) |
| **Quan et al. (2018)** | Mixed (including lung, colorectal, liver, breast cancers) | RCT | 43 (21/22); 60.04 ± 10.02 years | 1) Modified Shanggan fuzi decoction (100 ml, p.o., b.i.d.) 2) Morphine sulfate controlled-release tablets (10-20 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) 2) Duration of pain relief (p < 0.05) | 4 weeks | E: 11 cases (9 constipation, 2 nausea and vomiting) C: 32 cases (23 constipation, 9 nausea and vomiting) |
| **Liu (2020)** | Rectal cancer | RCT | 30 (17/13); 60.6 ± 5.4 years | 1) Lihuhui decoction (150 ml, p.o., b.i.d.) 2) Irinotecan hydrochloride (40 mg, i.v., first treatment) 3) Capecitabine (500 mg, p.o., b.i.d.) | 1) Response rate (p < 0.05) 2) Pain intensity (p < 0.05) | 6 weeks | NR |
| **Yang (2020)** | Mixed (including lung primary cancer) | RCT | 35 (17/13); 56.98 ± 3.62 years | 1) EAHM formula for individual research (200 ml, p.o., b.i.d.) 2) Zoledronic acid with normal saline tablets (100 ml, 40 mg, i.v., first treatment) | 1) Response rate (p < 0.05) 2) Pain intensity (p < 0.05) | 2 weeks | E: 4 cases (1 fever, 1 bone joint pain, 2 gastrointestinal reaction) C: 3 cases (1 fever, 1 bone joint pain, 1 gastrointestinal reaction) |

(Continued on following page)
TABLE 1 | (Continued) Characteristics of included studies.

| First author (Year) | Type of cancer | Trial design | Number of participants (male/ female); age (mean ± SD) | Interventions | Outcome index (intergroup differences p-value) | Course of treatment | Adverse event (case/symptom) |
|---------------------|----------------|--------------|------------------------------------------------------|---------------|-----------------------------------------------|--------------------|----------------------------|
| Liang et al. (2021)  | Mixed (including lung, gastric, liver, colon, breast, cervical cancers) | RCT | 39 (23/16); 59.6 ± 7.5 years | 1) Crocinobetalactam capsules (0.5 g, p.o., t.i.d.) 2) WHO 3-step analgesic ladder treatment: diclofenac sodium sustained-release tablets (1 t, p.o., q.d.); profenbeine sustained-release tablets (2-4 t, p.o., b.i.d.); morphine sulfate sustained-release tablets (1-2 t, p.o., b.i.d.) | 1) WHO 3-step analgesic ladder treatment: diclofenac sodium sustained-release tablets (1 t, p.o., q.d.); profenbeine sustained-release tablets (2-4 t, p.o., b.i.d.); morphine sulfate sustained-release tablets (1-2 t, p.o., b.i.d.) | 4 weeks | E: 34 cases (14 anorexia, 14 constipation, 6 vomiting); C: 67 cases (23 anorexia, 24 constipation, 20 vomiting) |

2017b; Chen et al., 2017; Bao, 2018; Dong et al., 2018; Miu and Quan, 2018; Ouyang, 2018; Liu, 2020; Yang, 2020; Liang et al., 2021). The screening process is summarized in the PRISMA 2020 flow diagram (Figure 1).

3.2 Study Characteristics
The basic characteristics of the 38 included studies are summarized in Table 1. Only one study was published in English and the rest were published in Chinese. All studies were conducted in China. In general, 3434 patients with cancer pain were included. The sample size ranged from 30 to 320 participants. In the treatment groups, 28 studies used ECCM (Lin et al., 2001; Chen et al., 2005; Cao and Xu, 2006; Zhang et al., 2006; Chen, 2009; Hao, 2009; Zhang et al., 2009; Cai, 2010; Li et al., 2010; Fu, 2011; He, 2012; Jiang et al., 2013; Wang and Chen, 2013; Chen H. et al., 2014; Liu and Zhou, 2014; Wan et al., 2014; Li et al., 2017b; Chen et al., 2017; Bao, 2018; Dong et al., 2018; Miu and Quan, 2018; Ouyang, 2018; Liu, 2020; Yang, 2020; Liang et al., 2021), and 10 studies used EAHM alone (Zhang, 2001; Li et al., 2002; Ma et al., 2003; Wu et al., 2005; Zhai et al., 2009; Zhang, 2009; Wang et al., 2011; Zhou, 2011; Cheng et al., 2012; Meng, 2012). In terms of control conditions, all included studies used CM, such as WHO 3-step ladder, opioids, and other analgesics. Outcomes on the efficacy of EAHM were reported in all 38 included studies. Response rate was reported as the primary outcome measure in 37 studies (Lin et al., 2001; Zhang, 2001, 2009; Li et al., 2002, 2010, 2017a, 2017b; Ma et al., 2003; Chen, 2004, 2009; Chen et al., 2005, Chen H. et al., 2014, 2017; Wu et al., 2005; Cao and Xu, 2006; Zhang et al., 2006, 2009; Hao, 2009; Zhai et al., 2009; Cai, 2010; Fu, 2011; Wang et al., 2011; Zhou, 2011; Cheng et al., 2012; He, 2012; Meng, 2012; Jiang et al., 2013; Wang and Chen, 2013; Wan et al., 2014; Bao, 2018; Dong et al., 2018; Miu and Quan, 2018; Ouyang, 2018; Liu, 2020; Yang, 2020; Liang et al., 2021). Continuous pain intensity, another primary outcome measure, was reported in 12 studies (Ma et al., 2003; Zhai et al., 2009; Meng, 2012; Jiang et al., 2013; Song et al., 2015; Li et al., 2017a, 2017b; Dong et al., 2018; Miu and Quan, 2018; Liu, 2020; Yang, 2020; Liang et al., 2021). In terms of secondary outcome measures, duration of pain relief was observed in 9 studies (Lin et al., 2001; Wu et al., 2005; Cao and Xu, 2006; Chen, 2009; Li et al., 2017a; Li et al., 2017b; Dong et al., 2018; Ouyang, 2018). Performance status was observed in 7 studies (Chen et al., 2005, 2017; Li et al., 2017a, 2017b; Dong et al., 2018; Miu and Quan, 2018; Liang et al., 2021); opioid usage was observed in 3 studies (Li et al., 2017a, 2017b; Dong et al., 2018). Adverse events were reported in 30 studies (Lin et al., 2001; Zhang, 2001; Li et al., 2002; Chen et al., 2005; Wu et al., 2005; Cao and Xu, 2006; Zhang et al., 2006; Zhai et al., 2009; Chen, 2009; Zhang, 2009; Wang et al., 2011; Zhou, 2011; Cheng et al., 2012; He, 2012; Meng, 2012; Wang and Chen, 2013; Chen H. et al., 2014; Wan et al., 2014; Song et al., 2015; Li et al., 2017a; Li et al., 2017b; Bao, 2018; Dong et al., 2018; Miu and Quan, 2018; Ouyang, 2018; Yang, 2020; Liang et al., 2021).

3.3 Risk of Bias
The methodological quality of 38 included studies is summarized in Table 2. The risk of bias of studies was assessed using the Rob 2.0 tool (Sterne et al., 2019). In domain 2, bias due to deviations from intended interventions, the risk of bias in all studies was rated high. Although all included studies declare randomization, no study adopted the double-blind method, and this is because the subject and the provider of the intervention can be aware of the assigned intervention. On the other hand, almost all studies did not report on the specific randomization method, and all included studies did not have a registered protocol. Consequently, it was impossible to evaluate compliance with the pre-planned statistical analysis method. Therefore, domain 1 and domain 5 were also evaluated as having some concern of risk of bias in most included studies.
3.4 Primary Outcomes

3.4.1 Response Rate

Response rate was reported in 37 included trials. Meta-analysis of 26 trials (Lin et al., 2001; Chen, 2004; Chen et al., 2005; Cao and Xu, 2006; Chen, 2009; Hao, 2009; Zhang et al., 2009; Cai, 2010; Li et al., 2010; Fu, 2011; He, 2012; Jiang et al., 2013; Wang and Chen, 2013; Chen H. et al., 2014; Wan et al., 2014; Chen et al., 2017; Li et al., 2017a; Li et al., 2017b; Bao, 2018; Dong et al., 2018; Miu and Quan, 2018; Liu and Zhou, 2019; Liu, 2020; Yang, 2020; Liang et al., 2021) comparing ECCM with CM revealed a significant effect of ECCM in response rate (26 trials, n = 2127; RR: 1.06; 95% CI: 1.04 to 1.09, I² = 21%, p < 0.0001; Figure 2A). However, there is no significant difference between EAHM and CM on response rate (10 trials, n = 867; RR: 1.03; 95% CI: 0.99 to 1.07, I² = 0%, p = 0.1654; Figure 3A).

A visual summary of the confidence level for individual studies and pooled estimates using the response rate as the primary outcome was presented through a drapery plot (Figure 4A, Figure 5A).

3.4.2 Continuous Pain Intensity

Continuous pain intensity was measured in 12 included trials. In 9 studies (Jiang et al., 2013; Song et al., 2015; Li et al., 2017a; Li et al., 2017b; Dong et al., 2018; Miu and Quan, 2018; Liu, 2020; Yang, 2020; Liang et al., 2021) comparing ECCM with CM, ECCM was found to be significantly less effective in continuous pain intensity than CM (9 trials, n = 941, SMD: −1.74; 95% CI: −2.17 to −1.30; I² = 87%, p < 0.0001; Figure 2B). Compared with CM, EAHM exhibited significant improvement on continuous pain intensity (3 trials, n = 273, SMD: −0.50; 95% CI: −0.74 to −0.26; I² = 0%, p < 0.0001; Figure 3B). A visual

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**TABLE 2 | Methodological quality of the included studies according to the risk of bias 2.0.**

| First author (Year) | D1  | D2  | D3  | D4  | D5  | Overall |
|---------------------|-----|-----|-----|-----|-----|---------|
| Lin et al. (2001)   | Sc  | H   | L   | L   | Sc  | H       |
| Zhang (2001)        | Sc  | H   | L   | L   | Sc  | H       |
| Li et al. (2002)    | Sc  | H   | L   | L   | Sc  | H       |
| Ma et al. (2003)    | Sc  | H   | L   | L   | Sc  | H       |
| Chen (2004)         | Sc  | H   | L   | L   | Sc  | H       |
| Chen et al. (2005)  | Sc  | H   | L   | L   | Sc  | H       |
| Wu et al. (2005)    | Sc  | H   | H   | L   | H   | H       |
| Cao and Xu (2006)   | Sc  | H   | L   | H   | Sc  | H       |
| Zhang et al. (2006) | Sc  | H   | L   | L   | Sc  | H       |
| Chen (2009)         | Sc  | H   | L   | L   | Sc  | H       |
| Hao (2009)          | Sc  | H   | L   | L   | Sc  | H       |
| Zhai et al. (2009)  | Sc  | H   | L   | L   | Sc  | H       |
| Zhang (2009)        | Sc  | H   | L   | L   | Sc  | H       |
| Zhang (2009)        | Sc  | H   | L   | L   | Sc  | H       |
| Cai (2010)          | Sc  | H   | L   | L   | Sc  | H       |
| Li et al. (2010)    | Sc  | H   | L   | L   | Sc  | H       |
| Fu (2011)           | Sc  | H   | L   | L   | Sc  | H       |
| Wang et al. (2011)  | Sc  | H   | L   | L   | Sc  | H       |
| Zhou (2011)         | Sc  | H   | L   | L   | Sc  | H       |
| Cheng et al. (2012) | Sc  | H   | H   | L   | Sc  | H       |
| He (2012)           | Sc  | H   | L   | L   | Sc  | H       |
| Meng (2012)         | Sc  | H   | L   | L   | Sc  | H       |
| Jiang et al. (2013) | Sc  | H   | L   | L   | Sc  | H       |
| Wang S. J. et al. (2013) | Sc  | H   | L   | L   | Sc  | H       |
| Chen H. et al. (2014) | Sc  | H   | L   | L   | Sc  | H       |
| Liu and Zhou (2014) | Sc  | H   | L   | L   | H   | H       |
| Wan et al. (2014)   | Sc  | H   | L   | L   | Sc  | H       |
| Song et al. (2015)  | Sc  | H   | H   | L   | H   | H       |
| Chen et al. (2017)  | Sc  | H   | L   | L   | Sc  | H       |
| Li et al. (2017a)   | Sc  | H   | L   | L   | Sc  | H       |
| Li et al. (2017b)   | Sc  | H   | L   | L   | Sc  | H       |
| Bao (2018)          | Sc  | H   | L   | H   | Sc  | H       |
| Dong et al. (2018)  | Sc  | H   | L   | L   | Sc  | H       |
| Miu and Quan (2018) | Sc  | H   | L   | L   | Sc  | H       |
| Ouyang (2018)       | Sc  | H   | L   | L   | Sc  | H       |
| Liu (2020)          | Sc  | H   | L   | L   | Sc  | H       |
| Yang (2020)         | Sc  | H   | L   | L   | Sc  | H       |
| Liang et al. (2021) | Sc  | H   | L   | L   | Sc  | H       |

D1-D5: 5 domain criteria.
D1: bias arising from the randomization process; D2: bias due to deviations from intended interventions; D3: bias due to missing outcome data; D4: bias in the measurement of the outcome; D5: bias in the selection of the reported results.
H, high risk of bias; L, low risk of bias; Sc, Some concerns.
summary of the confidence level for individual studies and pooled estimates using the continuous pain intensity as primary outcome was presented through a drapery plot (Figure 4B, Figure 5B).

### 3.5 Secondary Outcomes

#### 3.5.1 Duration of Pain Relief

Duration of pain relief was reported in 7 trials (Lin et al., 2001; Cao and Xu, 2006; Chen, 2009; Li et al., 2017a; Li et al., 2017b; Dong et al., 2018; Ouyang, 2018) that compared ECCM with CM. The meta-analysis showed a significant enhancement by ECCM in duration of pain relief (7 trials, n = 838, SMD: 0.96, 95% CI: 0.69 to 1.22; I² = 69%, p < 0.0001; Figure 6A). However, no significant statistical difference was identified in 1 trial measuring the effect of EAHM on the duration of pain compared to the CM (1 trial, n = 55, SMD: -0.09; 95% CI: -0.62 to 0.45; p > 0.05) (Wu et al., 2005).

#### 3.5.2 Performance Status

Seven trials measured the effect of ECCM on performance status compared with CM. The meta-analysis revealed a significant improvement in performance status by ECCM (7 trials, n = 746, WMD: 10.71; 95% CI: 4.89 to 16.53; I² = 97%, p = 0.0003; Figure 6B).
3.5.3 Opioid Usage

Opioid usage was measured in three trials that compared ECCM with CM. The meta-analysis showed a significant reduction by ECCM in opioid usage (3 trials, \( n = 540; \) WMD: \(-20.66\) mg/day; 95% CI: \(-30.22\) to \(-11.10; I^2 = 89\%, \ p < 0.0001; Figure 6C).

3.5.4 Adverse Events

In total, 30 trials (30/38, 78.94%) (Lin et al., 2001; Zhang, 2001; Li et al., 2002; Chen et al., 2005; Wu et al., 2005; Cao and Xu, 2006; Zhang et al., 2006; Chen, 2009; Zhai et al., 2009; Zhang, 2009; Zhang et al., 2009; Fu, 2011; Wang et al., 2011; Zhou, 2011; Cheng et al., 2012; Meng 2012) reported information on adverse events (AEs). The side effects that occur during the treatment of cancer pain are mainly reported in three areas: upper alimentary tract reactions including nausea and vomiting, lower gastrointestinal tract reactions, such as constipation and diarrhea, and neurologic symptoms such as drowsiness, dizziness, and headache (Scarborough and Smith, 2018). Accordingly, the incidence rates between groups were compared by dividing the findings of AEs reported into the above-mentioned three categories and one category including other symptoms such as burning sensation, fever, fatigue, hypocalcemia, and pruritus in this study. Considering that more than one AE is observed in one patient, if there are several types of AEs observed within an individual symptom category, the type of measurement findings and the number of subjects in each group were multiplied for analysis. Meta-analysis of the upper alimentary tracts’ reaction category showed that the use of EAHM or ECCM significantly reduced the incidences of AEs (20 trials; OR: 0.36; 95% CI: 0.29 to 0.45; \( p < 0.0001; \) Supplementary Figure S3A). The aggregated results of the lower intestinal tracts reaction category suggested that the incidence of AEs was significantly reduced by ECCM or EAHM (16 trials; OR: 0.32; 95% CI: 0.24 to 0.44; \( p < 0.0001; \) Supplementary Figure S3B). In addition, the meta-analysis showed that administration of EAHM alone or in combination with CM could reduce the incidence of AEs in the neurologic symptoms category (9 trials; OR: 0.74; 95% CI: 0.28 to 0.74; \( p < 0.0001; \) Supplementary Figure S3C) and other symptom categories. (12 trials; OR: 0.40; 95% CI: 0.24 to 0.65; \( p < 0.0001; \) Supplementary Figure S3D). All the reported AEs were not severe and disappeared without long-term treatment. The details of adverse events reported for each study are recorded in Table 1.

3.6 Meta-Regression and Subgroup Analysis

As a result of nine trials comparing the effects of continuous pain intensity between ECCM and CM, Higgins \( I^2 \) was 87%, suggesting heterogeneity. Therefore, meta-regression was performed on this result to search for a moderator that induces a potential cause of heterogeneity. As potential moderators, type of cancer, use of opioids in the control group, and duration of treatment were
assumed. As a result of meta-regression, there was no statistically significant difference between mixed cancer and single cancer type subgroups ($p = 0.535$), but significant statistical differences were confirmed between subgroups according to whether opioids were adopted in the control group ($p = 0.003$). Moreover, there was a statistically significant difference between the subgroup with a treatment duration of 2 weeks or more and the subgroup with a treatment duration of 2 weeks or less ($p = 0.034$). These results are shown in the bubble plot (Supplementary Figures S4A–C). However, a moderator affecting heterogeneity was not identified in the subgroup analysis, as shown in Table 3. For other outcome measurements, additional subgroup analysis could not be attempted due to the low heterogeneity or the very small number of included studies.

FIGURE 4 | Drapery plot of the trials that compared ECOM with CM alone for (A) response rate and (B) pain intensity.
3.7 Quality of Evidence According to Outcome Measures
In the comparison between ECCM and CM, the overall quality of evidence according to all outcome measures was low. Meanwhile, in EAHM monotherapy compared with CM, the overall quality of evidence according to all outcome measures was low to moderate. The results of the GRADE assessment are presented in Table 4.

3.8 Publication Bias
Contour-enhanced funnel plot analysis was performed to explore publication bias through the response rate, which is the outcome covering the most included studies. As shown in Figure 7, the pattern in the funnel plot, including 37 studies, showed obvious asymmetry, indicating that there might have been publication bias. This was further confirmed by Egger’s test ($p < 0.0001$) and Begg’s test ($p = 0.0013$).

FIGURE 5 | Drapery plot of the trials that compared EAHM with CM for (A) response rate and (B) pain intensity.
3.9 Association Rule Mining of EAHM Ingredients

3.9.1 Detailed Information and Distribution of EAHM Ingredients

A total of 125 herbs were used in 38 studies included in this review. Detailed information and types of preparations of herbs constituting EAHM prescriptions are summarized in Table 5. Among them, the top 10 most frequently prescribed herbs for cancer pain were *Glycyrrhiza uralensis* Fisch. ex DC. [Fabaceae], *Paeonia lactiflora* Pall. [Paeoniaceae], *Angelica sinensis* (Oliv.) Diels [Apiaceae], *Prunus persica* (L.) Batsch [Rosaceae], *Corydalis ternata* (Nakai) Nakai [Papaveraceae], *Carthamus tinctorius* L. [Asteraceae], *Pinellia ternata* (Thunb.) Makino [Araceae], *Cullen corylifolium* (L.) Medik. [Fabaceae], *Buthus martensi* Karsch, and *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae]. The relative frequencies of the herb ingredients, which were used in the top 10, ranged from 21.05% to a maximum of 52.63%. The frequency distribution of herbs is shown in Table 6.
| Intervention and comparator intervention | Outcomes | Number of participants (studies) | Anticipated absolute or relative effects (95% CI) | Quality of the evidence (GRADE) |
|-----------------------------------------|----------|----------------------------------|-----------------------------------------------|-------------------------------|
| ECCM compared to CM for cancer pain    | Response rate | 2127 (26 RCTs) | RR 1.06 more (1.04 more to 1.09 more) | eeeO MODERATE<sup>a</sup> |
|  | Continuous pain intensity | 841 (9 RCTs) | SMD 1.74 SD lower (2.17 lower to 1.3 lower) | eeeO LOW<sup>b</sup> |
|  | Duration of pain relief | 838 (7 RCTs) | SMD 0.93 SD higher (0.67 higher to 1.2 higher) | eeeO LOW<sup>b</sup> |
|  | Performance status | 746 (7 RCTs) | MD 10.71 higher (4.89 higher to 16.53 higher) | eeeO LOW<sup>b</sup> |
|  | Opioid usage | 540 (3 RCTs) | MD 20.66 lower (30.22 lower to 11. lower) | eeeO LOW<sup>b</sup> |
| EAHM monotherapy compared CM for cancer pain | Response rate | 867 (10 RCTs) | RR 1.03 (0.99–1.07) | eeeO VERY<sup>abc</sup> |
|  | Continuous pain intensity | 273 (3 RCTs) | SMD 0.5 SD lower (0.74 lower to 0.26 lower) | eeeO LOW<sup>b,c</sup> |
|  | Duration of pain relief | 55 (1 RCT) | SMD 0.18 SD higher (0.18 lower to 0.53 higher) | eeeO VERY<sup>abc</sup> |

EAHM, East Asian herbal medicine; ECCM, East Asian herbal medicine combined conventional medicine; CM, conventional medicine; MD, mean difference; RR, risk ratio; RCT, randomized clinical trial; SD, standardized difference; SMD, standardized mean difference.

GRADE, working group grades of evidence.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: very uncertain about the estimate.

<sup>a</sup>Study design with some bias in randomized or distributed blind.

<sup>b</sup>The confidence intervals are less overlapping, and the heterogeneity is high.

<sup>c</sup>The 95% confidence interval passes 0 (MD and SMD) or 1 (RR and OR) and the other interventions (OIs) are not satisfied.

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**TABLE 4** | Summary of findings for studies in this meta-analysis.

**FIGURE 7** | Contour-enhanced funnel plot of the trials for response rate.
### TABLE 5 | The ingredients of EAHM used in the included studies.

| Study        | EAHM prescription name         | Source                        | Ingredients of EAHM prescription (Latin name)                                                                                                                                                                                                 | Ingredients of EAHM prescription (Scientific name)                                                                 | Types of preparation | Quality control reported (Y/N) | Chemical analysis reported (Y/N) |
|--------------|-------------------------------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------|---------------------------------|
| Lin et al.   | Jiawei niantong capsule       | Prepared by Lin et al. (2001) | Corydalis Tuber, Cyprip Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeaceae], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Zhang (2001) | Compound Strychnos capsule    | Prepared by Zhang (2001)      | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeaceae], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Li et al.    | Tribal medicina Duwkei        | Prepared by Li et al. (2002)  | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeaceae], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Ma et al.    | Jiaweibaoankeli               | Prepared by Ma et al. (2003)  | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeacee], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Chen (2004)  | Shitong decoction             | Prepared by Chen (2004)       | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeacee], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Chan et al.  | Zhitong capsule               | Prepared by Chan et al. (2005) | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeacee], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Wu et al.    | Alonggong capsule            | Prepared by Wu et al. (2005)  | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeacee], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Cao and Xu   | Zhonggu Zhtong Powder         | Prepared by Cao and Xu (2006) | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeacee], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |
| Zhang et al. | EAHM formula for individual research | Prepared by Zhang et al. (2006) | Corydalis Tuber, Cyperi Rhizoma, Notoginseng Radix et Rhizoma, Aquilaria Lignum, Curcumaee Rhizoma, Ophi Urticae Peripanicum, Nardostachys Radix et Rhizoma, Chinannes, Rhei Radix et Rhizoma, Borneolum                              | Corydalis tetara (Nakai) Nakai [Papaveraceae], Cypripodorus nudus L. [Cypripodaceae], Panax notoginseng (Burkill) F.H.Chen [Araliaceae], Aquilaria malaccensis Lam. [Thymelaeacee], Curcuma phanaeaceae Valton [Zingiberaceae], Citrus deliciosa Ten. [Rutaceae], Nardostachys paniculata (D.Don) DC. [Orobanchaceae], Dracaena cinnabari Battf. [Asparagaceae], Rhumum palluitum L. [Polygonaceae], Dryobalanops aromatica C.F.Gaertn. [Dipterocarpacea] | Capsule              | N                              | N                              |

(Continued on following page)
| Study                          | EAHM prescription name               | Source                                      | Ingredients of EAHM prescription (Latin name)                                                                 | Types of preparation | Quality control reported? | Chemical analysis reported? |
|-------------------------------|--------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------|---------------------------|-----------------------------|
| Chen (2009)                   | Novel Shantong Zhuwu decoction       | Prepared by Chen (2009)                     | Gentiana macrophylla Radix 12 g, Crinum orientale 12 g, Pericallis Semen 12 g, Carthamus Sins 9 g, Glycyrrhiza Radix et Rhizoma 6 g, Osorini subbotanepuri Radix et Rhizoma 9 g, Myrrha 9 g, Angelicae Seminis Radix 15 g, Foeniculum vulgare Foeniculum 9 g, Aconitum Radix 15 g, Microsperma ovari 9 g, Scopolam Alocasia 2 pieces, Scoporia 10 g, Poriae Semen 15 g, Drynariae Radix 15 g, Herba Bupleuri Tubo 10 g, Glycyrrhizae Radix et Rhizoma 10 g | Decoction           | N                          | N                           |
| Zhai et al. (2009)            | Anti-cancer Zhong decoction          | Prepared by Zhai et al. (2009)              | Gentiana macrophylla Radix 12 g, Cnidii Rhizoma 12 g, Prunus persica (L.) Batsch [Rosaceae] 12 g, Carthamus Lutescens L., Artemisiae lutea Radix, ex DC., Ficariae tauri 9 g, Ovarum grossirepentis (Milw.) Rau 9 g, Cnini phytolaxis (F. Ch.) Eng. [Brassicaceae] 9 g, Angelicae sinensis (Oliv.) Wolf 9 g, Gardeniae fructus 9 g, Stephaniae tuber 9 g, Piperis ischaemum 9 g, Citri trifoliata 9 g, Ziziphi Fructus 9 g | Decoction           | N                          | N                           |
| Hao (2009)                    | EAHM formula for individual research | Prepared by Hao (2009)                      | Gentiana macrophylla Radix 12 g, Cnidii Rhizoma 12 g, Prunus persica (L.) Batsch [Rosaceae] 12 g, Carthamus Lutescens L., Artemisiae lutea Radix, ex DC., Ficariae tauri 9 g, Ovarum grossirepentis (Milw.) Rau 9 g, Cnini phytolaxis (F. Ch.) Eng. [Brassicaceae] 9 g, Angelicae sinensis (Oliv.) Wolf 9 g, Gardeniae fructus 9 g, Stephaniae tuber 9 g, Piperis ischaemum 9 g, Citri trifoliata 9 g, Ziziphi Fructus 9 g | Decoction           | N                          | N                           |
| Zhang (2009)                  | Tung powder                          | Prepared by Zhang (2009)                     | Gentiana macrophylla Radix 12 g, Cnidii Rhizoma 12 g, Pericallis Semen 12 g, Carthamus Sins 9 g, Glycyrrhiza Radix et Rhizoma 6 g, Osorini subbotanepuri Radix et Rhizoma 9 g, Myrrha 9 g, Angelicae Seminis Radix 15 g, Foeniculum vulgare Foeniculum 9 g, Aconitum Radix 15 g, Microsperma ovari 9 g, Scopolam Alocasia 2 pieces, Scoporia 10 g, Poriae Semen 15 g, Drynariae Radix 15 g, Herba Bupleuri Tubo 10 g, Glycyrrhizae Radix et Rhizoma 10 g | Decoction           | N                          | N                           |
| Zhang et al. (2009)           | Wendan decoction                     | Prepared by Zhang et al. (2009)             | Gentiana macrophylla Radix 12 g, Cnidii Rhizoma 12 g, Pericallis Semen 12 g, Carthamus Sins 9 g, Glycyrrhiza Radix et Rhizoma 6 g, Osorini subbotanepuri Radix et Rhizoma 9 g, Myrrha 9 g, Angelicae Seminis Radix 15 g, Foeniculum vulgare Foeniculum 9 g, Aconitum Radix 15 g, Microsperma ovari 9 g, Scopolam Alocasia 2 pieces, Scoporia 10 g, Poriae Semen 15 g, Drynariae Radix 15 g, Herba Bupleuri Tubo 10 g, Glycyrrhizae Radix et Rhizoma 10 g | Decoction           | N                          | N                           |

(Continued on following page)
| Study | EAHM prescription name | Source | Ingredients of EAHM used in the included studies. | Types of preparation | Quality control reported? | Chemical analysis reported? |
|-------|------------------------|--------|--------------------------------------------------|---------------------|--------------------------|---------------------------|
| Cai (2011) Yanghe decoction | Prepared by Cai (2011) | Rhei Radix Preparata 30 g, Cinnamomi Cortex 9 g, Ephedrae Herba 9 g, Corydalis Tuber 15 g, Cinnamomi Cortex Interior 15 g, Caudis Sargentioda 30 g, Magnoliae Cortex 30 g, Rhei Radix et Rhizoma 15 g, Coicis Semen 30 g, Paeoniae Rhizoma 30 g | Decotion | N | N |
| Li et al. (2010) Taohongsiwu decoction | Prepared by Li et al. (2010) | Poriae Semen 20 g, Pinelliae Rhizoma 20 g, Pinelliae Tuber 10 g, Pinelliae Tuber 10 g, Paeoniae Radix 20 g | Decotion | N | N |
| Fu (2011) Qigetongbu decoction | Prepared by Fu (2011) | Astragalus Mongholicus Bunge [Fabaceae] 30 g, Poriae Semen 20 g, Pinelliae Rhizoma 20 g, Paeoniae Radix 20 g, Glyceriae Uralensis Fisch. ex DC. 30 g | Decotion | N | N |
| Wang et al. (2011) EAHM formula for individual research | Prepared by Wang et al. (2011) | Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g | Decotion | N | N |
| Zhou (2011) Tuij powder | Prepared by Zhou (2011) | Scopoliandra 30 g, Curcumae Radix 30 g, Scopoliandra 30 g, Curcumae Radix 30 g, Scopoliandra 30 g, Curcumae Radix 30 g, Scopoliandra 30 g | Powder | N | N |
| Chang et al. (2012) Baishu Ruid decoction | Prepared by Chang et al. (2012) | Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g | Decotion | N | N |
| He (2012) EAHM formula for individual research | Prepared by He (2012) | Astragalus Mongholicus Bunge [Fabaceae] 30 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g, Aconiti Lateralis Radix Preparata 10 g | Decotion | N | N |

(Continued on following page)
TABLE 5 | (Continued) The ingredients of EAHM used in the included studies.

| Study | EAHM prescription name | Source | Ingredients of EAHM prescription (Latin name) | Ingredients of EAHM prescription (Scientific name) | Types of preparation | Quality control reported? | Chemical analysis reported? |
|-------|------------------------|--------|--------------------------------|-------------------------------------------------|-------------------|------------------|------------------|
| Meng (2012) | EAHM formula for individual research | Prepared by Meng (2012) | Astragalus Radix 30 g, Mellea Fructus 10 g, Pteleaee Tuber 10 g, Phelodendri Cortex 15 g, Paeoniae Radix 30 g, Pinelliae Tuber 15 g, Paeoniae Radix 30 g, Pteleaee Tuber 10 g, Pteleaee Tuber 15 g, Scrophulariae Radix 12 g, Glycyrrhizae Radix et Rhizoma 10 g, Peoniae Radix 6 g, Liriope 15 g | Asparagus equatorius (Burkill) F.H.Chen 30 g, Mellea azadirach L. [Meliaceae] 10 g, Pteleaee Tuber (Thunb.) Makino [Pseudo] 10 g, Phelodendri Cortex Don [Cannabinacae] 30 g, Pteleaee Tuber Chen (2012) EAHM formula for individual Prepared by Chen (2012) | Decoction | N | N |
| Jiang et al. (2013) | EAHM formula for individual research | Prepared by Jiang et al. (2013) | Hedyotidis Herba 15 g, Scutellariae Barbatae Herba 20 g, Rheum palmatum L. 15 g, Astragali Radix 20 g, Codonopsis pilosula (Franch.) Nannf. 20 g, Paeoniae Radix 20 g, Rehmanniae Radix 20 g, Curcumae Rhizoma 12 g, Ponciri Fructus Immaturus 12 g | Gynostemma pentaphyllum (Thunb.) Makino [Cucurbitaceae] 30 g, Pteleaee Tuber 15 g, Loranthi Ramulus et Folium 15 g, Glycyrrhizae Radix et Rhizoma 10 g, Peoniae Radix 6 g, Liriope 15 g | Decoction | N | N |
| Wang and Chen (2013) | GeLiu Zhiyu decoction combined Shizao powder | Prepared by Wang and Chen (2013) | Typhoe Pollen 6 g, Tropaeolus flavescens 6 g, Liriope 15 g, Paeoniae Radix 12 g, Scrophulariae Radix 12 g, Glycyrrhizae Radix et Rhizoma 10 g | Gynostemma pentaphyllum (Thunb.) Makino [Cucurbitaceae] 30 g, Pteleaee Tuber 15 g, Loranthi Ramulus et Folium 15 g, Glycyrrhizae Radix et Rhizoma 10 g | Decoction | N | N |
| Chen H. et al. (2014) | Xuefu Zhiyu decoction | Prepared by Chen H. et al. (2014) | Paeoniae Semen 20 g, Carthami Flos 9 g, Angelicae Sinensis Radix 9 g, Rehmanniae Radix 15 g, Codonopsis Radix 30 g, Licorici Radix 15 g, Liquiritiae Radix 15 g | Gynostemma pentaphyllum (Thunb.) Makino [Cucurbitaceae] 30 g, Pteleaee Tuber 15 g, Loranthi Ramulus et Folium 15 g, Glycyrrhizae Radix et Rhizoma 10 g | Decoction | N | N |
| Liu and Zhou (2014) | BuBu Huoxue decoction | Prepared by Liu and Zhou (2014) | Rehmanniae Radix Preparata 30 g, Rehmanniae Radix Fracta 30 g, Dioscoreae Rhizoma 20 g, Angelicae Sinensis Radix 30 g, Scrophulariae Radix 15 g, Liquidambari Fructus 10 g, Gynostemma pentaphyllum (Thunb.) Makino [Cucurbitaceae] 30 g, Pteleaee Tuber 15 g, Loranthi Ramulus et Folium 15 g, Glycyrrhizae Radix et Rhizoma 10 g | Gynostemma pentaphyllum (Thunb.) Makino [Cucurbitaceae] 30 g, Pteleaee Tuber 15 g, Loranthi Ramulus et Folium 15 g, Glycyrrhizae Radix et Rhizoma 10 g | Decoction | N | N |
| Study | EAHM prescription name | Source | Ingredients of EAHM prescription (Latin name) | Ingredients of EAHM prescription (Scientific name) | Types of preparation | Quality control reported? (Y/N) | Chemical analysis reported? (Y/N) |
|-------|------------------------|--------|---------------------------------------------|--------------------------------------------------|---------------------|-----------------------------|-------------------------------|
| Wan et al. (2014) | Compound Sangthi mixture | Prepared by Wan et al. (2014) | Mori Ramulius 30 g, Sinomeni Caulis et Rhizoma 30 g, Piperis Kaduare Caulis 30 g, Angelicae Sinesis Radix 15 g, Osteri ssa | Monus alba L. [Moraceae] 30 g, Sinomurium acutum (Thunb.) Reider & H.Wilson [Menispermacae] 30 g, Piper Kaduare (Ochoi) Ohwi [Piperaceae] 30 g, Angelicae sinensis (Ohwi) Delis [Apiaceae] 15 g, Osteri ssa proserusserum (Maxim) Kitag. [Apiaceae] 10 g, Aralia continentalis Kthag. [Araliaceae] 10 g, Gentiana macrophylla Pall. [Gentianaceae] 10 g, Sinomurium acutum (Thunb.) Reider & E.H.Wilson [Menispermacae] 10 g, Clematis terniflora var. mandshurica (Fur.) Ohwi [Ranunculaceae] 10 g, Conomium anthriscoides [Chuanxiong] [Apiaceae] 12 g | Decotion | N | N |
| Song et al. (2018) | Bai Shao Zong Gan Jiao Nang | Commercial Supplier Ningbo Lihua Pharmacy Co. Ltd | Morus alba L. [Moraceae] 30 g, Piper kadsura (Choisy) Ohwi [Piperaceae] 30 g, Ostericum grosseserratum (Maxim.) Kitag. [Apiaceae] 10 g, Clematis terniflora var. mandshurica (Fur.) Ohwi [Ranunculaceae] 10 g, Conomium anthriscoides [Chuanxiong] [Apiaceae] 12 g | Paeonia lactiflora Pall. [Paeoniaceae] | Capsule | N | N |
| Chen et al. (2017) | Notopterygii Radix et Rhizoma | Prepared by Chen et al. (2017) | Araliae Continentalis Radix 10 g, Gentiana macrophylla Pall. [Gentianaceae] 10 g, Clematidis Radix 10 g, Cnidii Rhizoma 12 g | | | | |
| Li et al. (2017a) | Xuexu Zhuyu decoction | Prepared by Li et al. (2017a) | Angelicae Sinesis Radix 9 g, Rehmanniae Radix Recens 9 g, Paeoniae Radix 9 g, Persicae Semen 12 g, Carthami Flos 9 g, Adyshanae Radix 12 g, Buphthalmi Radix 6 g, Scophulariae Radix 6 g, Platycodonis Radix 6 g, Glycyrrhizae Radix et Rhizoma 6 g | | | | |
| Li et al. (2017a) | Gejia Zhuyu decoction | Prepared by Li et al. (2017a) | Trogonitores Faeoria 6 g, Angelicae Sinesis Radix 9 g, Paeoniae Radix 9 g, Persicae Semen 9 g, Carthami Flos 6 g, Scophulariae Radix 6 g, Undesiae Radix 6 g, Osteri ssa | | | | |
| Bao (2018) | Xuefu Zhuyu decoction | Prepared by Bao (2018) | Pericae Samen 20 g, Codonopsis Pilosulae Radix 15 g, Astragal Radix 15 g, Scophulariae Radix 10 g, Angelicae Sinesis Radix 10 g, Adyshanae Radix 9 g, Rehmanniae Radix Recens 9 g, Paeoniae Radix 6 g, Glycyrrhizae Radix et Rhizoma 6 g, Scophulariae Radix 6 g | | | | |
| Dong et al. (2018) | Huachansu Jiaonang | Commercial Supplier Eastarai pharmaceutical co,Ltd | Bufonis Venenum | | Capsule | N | N |
| Mu and Quan (2018) | Huachansu Jiaonang | Commercial Supplier Eastarai pharmaceutical co,Ltd | Bufonis Venenum | | Capsule | N | N | *(Continued on following page)*
| Study            | EAHM prescription name      | Source                                      | Ingredients of EAHM prescription (Latin name)                                                                 | Ingredients of EAHM prescription (Scientific name)                                                                 | Types of preparation | Quality control reported? (Y/N) | Chemical analysis reported? (Y/N) |
|------------------|-----------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------|----------------------------------|
| Ouyang (2018)    | Modified Shaogan Fuzi decoction | Prepared by Ouyang (2018)                   | Glycyrrhizae Radix et Rhizoma 20 g, Paeoniae Radix 60 g, Aconiti Lateralis Radix Preparata 15 g, Cuscutae Semen 20 g, Codonopsis Pilosulae Radix 20 g, Cannabis Semen 15 g, Curcumae Radix 10 g, Angelicae Sinensis Radix 10 g, Corydalis Tuber 15 g | Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae] 20 g, Paeonia lactiflora Pall. [Paeoniaceae] 60 g, Aconitum carmichaelii Debeaux [Ranunculaceae] 15 g, Cuscuta chinensis Lam. [Convolvulaceae] 20 g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae] 20 g, Cannabis sativa L. [Cannabaceae] 15 g, Curcuma aromatica Salisb. [Zingiberaceae] 10 g, Angelicae Semen 15 g, Delis [Apiaceae] 10 g, Corydalis tincturae (Nakai) Nesi. [Rubiaceae] 15 g | Decoction            | N                               | N                                |
| Liu (2020)       | Liujunzi decoction          | Prepared by Liu (2020)                      | Pseudostellariae Radix 15 g, Codonopsis Pilosulae Radix 15 g, Astragali Radix 30 g, Poria Sclerotium 15 g, Salviae Miltiorrhizae Radix 20 g, Dioscoreae Rhizoma 25 g, Atractylodes Rhizoma 15 g, Angelicae Sinensis Radix 15 g, Curcumae Radix et Rhizoma 25 g, Angelicae Semen 10 g, Saussurea Lappa 15 g, Curcuma aromatica Salisb. [Zingiberaceae] 10 g, Citri Unshius Pericarpium 15 g, Glycyrrhizae Radix et Rhizoma 25 g | Pseudostellaria heterophylla (Miq.) Pax [Caryophyllaceae] 15 g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae] 15 g, Astragalus mongholicus Bunge [Fabaceae] 30 g, Poria cocos Wolf 15 g, Scrophularia ophioglossoides (Willd.) R.J.Wang [Rubiaceae] 15 g, Salvia miltiorrhiza Bunge [Lamiaceae] 20 g, Dioscorea polystachya Turcz. [Dioscoreaceae] 25 g, Atractylodes macrocephala Koidz. [Asteraceae] 15 g, Angelicae Semen 15 g, Delis [Apiaceae] 15 g, Pinelliae tincturae (Thunb.) Makino (Anacardiaceae) 15 g, Paeonia lactiflora Pall. [Paeoniaceae] 15 g, Sparganium stoloniferum (Buch.-Ham. ex Graebn.) Buch.-Ham. ex Juz. [Typhaceae] 10 g, Curcuma phaeocaulis Valeton [Zingiberaceae] 15 g, Citrus deliciosa Ten. [Rutaceae] 15 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae] 25 g | Decoction            | N                               | N                                |
| Yang (2020)      | EAHM formula for individual research | Prepared by Yang (2020)                     | Astragali Radix 30 g, Platycodonis Radix 30 g, Trichosanthis Radix 30 g, Rhipani Semen 20 g, Salviae Sclerotium 15 g, Poria Sclerotium 15 g, Meliae Fructus 10 g, Pinelliae Tuber 10 g, Curcumae Radix et Rhizoma 25 g, Angelicae Semen 10 g, Saussurea Lappa 15 g, Curcuma aromatica Salisb. [Zingiberaceae] 10 g, Citri Unshius Pericarpium 15 g, Glycyrrhizae Radix et Rhizoma 25 g | Astragalus mongholicus Bunge [Fabaceae] 30 g, Platycodon grandiflorus (Jacq.) A.DC. [Campanulaceae] 30 g, Trichosanthis kirilowii Maxim. [Cucurbitaceae] 30 g, Poria Sclerotium 15 g, Meliae Fructus 10 g, Pinelliae Tuber 10 g, Curcumae Radix et Rhizoma 25 g, Angelicae Semen 10 g, Saussurea Lappa 15 g, Curcuma aromatica Salisb. [Zingiberaceae] 10 g, Citri Unshius Pericarpium 15 g, Glycyrrhizae Radix et Rhizoma 25 g | Decoction            | N                               | N                                |
| Liang et al. (2021) | Huachansu Jiaonang | Commercial Supplier Eastantai Pharmaceutical Co., Ltd. | Bufonis Venenum | Bufonis venenum Capsule N N | N |
3.9.2 Apriori Algorithm-Based Association Rule Analysis

Based on ingredient data from 38 EAHM formulations and 125 herbs included in this study, 10 association rules were identified in the analysis (Table 7). Based on the identified association rule, a scatter plot with support value on the x-axis and the confidence value on the y-axis was drawn to explore the distribution of lift values (Supplementary Figure S5). In this scatter plot, the depth of the dot color representing each association rule indicates the lift value. Through this, it was possible to observe the fact that the distribution of the overall lift value was distributed between 1.53 and 3.07. Meanwhile, a grouping matrix diagram was presented to examine the general distribution of the identified association rule (Supplementary Figure S6). The abscissas represent 7 clusters, and they represent items generated by 10 association rules. The depth of color inside the circle represents the degree of lift, and the circle size represents the degree of support. As a result of the above analysis, the three rules showing the highest support value of 2.37 were # 3 \{Prunus persica (L.) Batsch [Rosaceae]\} \(\Rightarrow\) \{Angelica sinensis (Oliv.) Diels [Apiaceae]\}, # 4 \{Prunus persica (L.) Batsch [Rosaceae]\} \(\Rightarrow\) \{Paeonia lactiflora Pall. [Paeoniaceae]\}, and # 5 \{Prunus persica (L.) Batsch [Rosaceae]\} \(\Rightarrow\) \{Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]\}. On the other hand, the rule showing the highest confidence value of 1.00 was #1 \{Scrophularia ningpoensis Hemsl. [Scrophulariaceae]\} \(\Rightarrow\) \{Paeonia lactiflora Pall. [Paeoniaceae]\}, and the herb patterns that can be predicted to increase the probability of significant association with lift value exceeding 2.0 are # 2 \{Carthamus tinctorius L. [Asteraceae]\} \(\Rightarrow\) \{Prunus persica (L.) Batsch [Rosaceae]\}, # 3 \{Prunus persica (L.) Batsch [Rosaceae]\} \(\Rightarrow\) \{Angelica sinensis (Oliv.) Diels\}, # 7 \{Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]\}, \{Prunus persica (L.) Batsch [Rosaceae]\} \(\Rightarrow\) \{Angelica sinensis (Oliv.) Diels [Apiaceae]\}, and \# 8 \{Angelica sinensis (Oliv.) Diels, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]\} \(\Rightarrow\) \{Prunus persica (L.) Batsch [Rosaceae]\}. Through the above analysis results, it was revealed that Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae], Angelica sinensis (Oliv.) Diels [Apiaceae], and Paeonia lactiflora Pall. [Paeoniaceae] were selected as the central herbs for treating cancer pain with a correlation with Prunus persica (L.) Batsch [Rosaceae]. However, since Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae] is also included in several other association rules, the potential core herb combination formed here could be regarded as Prunus persica (L.) Batsch [Rosaceae] - Angelica sinensis (Oliv.) Diels [Apiaceae] and Prunus persica (L.) Batsch [Rosaceae] - Paeonia lactiflora Pall. [Paeoniaceae]. Other influential herb pairs were Carthamus tinctorius L. [Asteraceae] - Prunus persica (L.) Batsch [Rosaceae] and Scrophularia ningpoensis Hemsl. [Scrophulariaceae] - Paeonia lactiflora Pall. [Paeoniaceae]. As a result, the herbs constituting the core ingredients of EAHM used in this study for cancer pain in patients were Prunus persica (L.) Batsch [Rosaceae], Angelica sinensis (Oliv.) Diels [Apiaceae], Carthamus tinctorius L. [Asteraceae], Paeonia lactiflora Pall. [Paeoniaceae], Scrophularia ningpoensis Hemsl. [Scrophulariaceae], and Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae]. The relationship of these association rules is presented through a network graph (Figure 8).

4 DISCUSSION

4.1 Summary of the Main Finding

In this systematic review, the effects and safety of EAHM as combined therapy or monotherapy versus conventional medicine for primary cancer pain were assessed. Overall, EAHM as combined therapy showed superior effects on cancer pain to those of conventional medicine in pain intensity, response rate, duration of pain relief, performance status, and opioid usage. Additionally, EAHM was generally safe and well-tolerable for patients with cancer. Patients treated with EAHM appeared to experience fewer incidence rates of AEs. Therefore, EAHM-combined therapy can be considered a worthy option based on the data of this study in the management of cancer pain. Regarding the various EAHM prescription data included in this study, as a result of the association rule mining, Prunus persica (L.) Batsch [Rosaceae], Angelica sinensis (Oliv.) Diels [Apiaceae], Carthamus tinctorius L. [Asteraceae], Paeonia lactiflora Pall. [Paeoniaceae], Scrophularia ningpoensis Hemsl. [Scrophulariaceae], and Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae] were identified as core herb ingredients. At the same time, four combinations of herb pairs considered to have potential significance for cancer pain were Prunus persica (L.) Batsch [Rosaceae] - Angelica sinensis (Oliv.) Diels [Apiaceae], Prunus persica (L.) Batsch [Rosaceae] - Paeonia lactiflora Pall. [Paeoniaceae], Carthamus tinctorius L. [Asteraceae] - Prunus persica (L.) Batsch [Rosaceae], and Scrophularia ningpoensis Hemsl. [Scrophulariaceae] - Paeonia lactiflora Pall. [Paeoniaceae]. Information on these core herbs is expected to have value as a useful hypothesis for future drug development research using EAHM.

4.2 Limitations

Clinicians and researchers should note the following limitations before utilizing the results of this systematic review. Firstly, the outcome measures that should be prioritized in pain management of various diseases, including cancer, is Minimum Clinically Important Difference (MCID) in continuous pain intensity. In particular, the significance of cancer pain is greater in that the severity of symptoms itself has a significant impact on the patient’s prognosis. However, in our review, only 12 studies measured continuous pain intensity, and MCID information was not addressed in any of the studies. The response rate adopted by many studies may be a criterion for determining whether an effect occurs, but it cannot replace MCID. For this reason, it is expected that more reliable EAHM efficacy for cancer pain will be possible only when more EAHM clinical trials considering MCID due to continuous pain intensity are conducted. Secondly, the effect of EAHM monotherapy on cancer pain examined in this study not only lacks evidence, despite some positive findings compared to conventional medicine but also lacks consistency in the reported results. Therefore, it was not possible to draw specific conclusions about the effects of EAHM monotherapy on cancer pain only.
from the studies included in this review. To solve this problem, clinical trials using placebo control and double-blind methodologies need to be additionally performed in the future. Thirdly, the methodological quality of the clinical trials included in this study is generally poor. It is believed that many studies lack explanations for random allocation concealment, cannot confirm pre-registered protocols, and do not employ blinding of participants and outcome assessors. For this reason, it is difficult to reach a rigorous conclusion even if the review includes relatively large sample data and primary tests. Therefore, until a clinical trial with an improved design is added, the conclusions of this review should be taken with caution, considering the information of individual included studies when used in clinical practice. Furthermore, high heterogeneity was observed in the continuous outcomes of this study. This heterogeneity reduces the strength of the synthesized evidence. In this review, meta-regression and subgroup analysis could be performed only on continuous pain intensity because only a few studies adopted a continuous outcome measure, and additional valuable information consistent with the characteristics of EAHM.

### 4.3 Implications of Clinical Practices

Evidence from the present study supports that concomitant use of EAHM may be considered for the management of cancer pain. The primary finding in this review supporting this is that EAHM as combined therapy provides a significant benefit in improving the response rate and pain intensity of cancer pain. This can be consistent with two previous systematic reviews of similar topics (Wang S.-J. et al., 2013; Lee et al., 2015). However, pain as the secondary symptom caused by anti-tumor treatment (e.g., surgery, chemotherapy, or radiotherapy) was excluded from the scope of the study, and pain caused by cancer itself was set as the target disease in this review. In addition, considering that EAHM is most widely used as a drug commonly taken orally, outcomes by topical applications such as injection, herbal bath, or herbal compression were not included. The characteristic of this review is that it is differentiated from previous studies related to the subject. In addition, considering that safety in cancer treatment is the major issue that patients are concerned about, the incidence rate of AEs was examined by category of symptoms and dosage of herbal formulations used in individual clinical trials. This leads to serious discrepancies between mediations except for the commonality of “East Asian herbal medicine combination.” In this review, association rule analysis was performed on herb data to overcome this heterogeneity problem partially and to derive more useful information. In the future systematic review of similar topics, it is expected that the data mining method will be actively used to derive additional valuable information consistent with the characteristics of EAHM.
adverse events through this analysis. These characteristics of our study suggested that the EAHM as combined therapy with a conventional approach may be a better strategy for cancer patients with pain who are partially insensitive to the conventional medicine alone or are intolerant to opioids and other analgesic drugs. However, a direct comparison between conventional medicine and EAHM showed a potentially better result in response rate but was not statistically significant. Regarding continuous pain intensity, EAHM monotherapy showed a significant lower effect, but the number of trials related to it was minimal. Therefore, it could not be concluded whether EAHM monotherapy can be used as an alternative to conventional treatment for the management of cancer pain.

In the herb data constituting the EAHM prescription of this study, four significant herb pairs and six high-frequency individual herbal medicines were identified. As seen in Table 7, the herbal medicines that form the core herb patterns in this study are expected to contribute to various findings of cancer patients not only in clinical research data but also in terms of mechanisms in modern pharmacological studies. In addition, the two-herb combination pattern identified in this study may be regarded as a frequently used herb pair due to their clinical value. EAHM is generally administered in the form of a multi-herb formula, and herb pairs are used as a basic unit for constructing patient-specific dosages and useful prescriptions (Wang et al., 2012). In addition, the herb pair concept has been widely used recently as a hypothesis to efficiently develop new drugs while reinterpreting existing clinical data from different angles by utilizing advanced research methodologies such as network pharmacology (Li et al., 2011; Mi et al., 2020). From this point of view, clinicians can incorporate the core herb combination information identified in this study into their decision-making.

4.4 Implications of Mechanism Research

The mechanism of action of EAHM, which solves various pathological problems in the human body at a systemic level through the action of multi-compounds on multi-targets, is being explored in more detail through recent scientific studies (Zhou et al., 2016). The multi-components of EAHM show a better effect by reducing toxicity and side effects due to the synergistic effect between various compounds in the process of acting on multiple targets. The concepts of “Gun-Shin-Jwa-Sa” (King-Retainer-Officer-Messenger, 君臣佐使 in Chinese characters) and herb pairs are the main prescribing principles of EAHM. To achieve the desired benefits and/or limit side effects of EAHM, use the “Gun-Shin-Jwa-Sa” principle. The key herb in an EAHM formula is “Gun,” which has a greater ratio of directly acting the disease. “Shin” is an adjuvant herb used to enhance the therapeutic impact of the main herb or to target the symptoms that come with it. “Jwa” is commonly used to reduce the EAHM formula’s negative effects. The herb “Sa” directs the active components to their intended organs or harmonizes their effects. Meanwhile, herb pair is a one-of-a-kind combination of two herbs that is the smallest unit of the EAHM formula and plays the most significant role in achieving synergy (Wang et al., 2012; Kim et al., 2015; Zhou et al., 2016). The four core herbal combination patterns explored in the results of this study, Prunus persica (L.) Batsch [Rosaceae] - Angelica sinensis (Oliv.) Diels [Apiaceae], Prunus persica (L.) Batsch [Rosaceae] - Paeonia lactiflora Pall. [Paeoniaceae], Carthamus...
It is also a predictable mechanism that the efficacy of individual drugs from different angles acts simultaneously, acting on the complex pathology of cancer pain. In the case of *Paeonia lactiflora* Pallas, it is already known that it has potential effectiveness in various types of cancer, such as bladder tumor and lung cancer, based on several mechanistic studies (Lin MY. et al., 2016; Ma et al., 2021). At the same time, the combination of *Paeonia lactiflora* Pall. [Paeoniaceae] and *Glycyrrhiza uralensis* Fisch. ex DC. [Fabaceae], which is one of the key herbs in this study, is the “Jakyak-Gamcho decoction” (Shaoyao-Gancao-Tang in Chinese and Shakuyaku-Kanzo-To in Japanese), which is supported by reports that the herb combination is involved in various pain, associated with signaling pathways through recent network pharmacology study (Lee et al., 2020). In the above, it has been elucidated that *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae], which forms a core combination with *Paeonia lactiflora* Pall. [Paeoniaceae], induces apoptosis of cancer cells by restoring anoikis sensitivity via disrupting focal adhesion action (Kim et al., 2017). As can be seen here, it is also important to specifically identify the pharmacological properties of individual drugs in order to select a meaningful core herbal combination. Considering *Prunus persica* (L.) Batsch [Rosaceae] contained in several core herb combinations, the active ingredient, which is amygdalin, is thought to contribute to the antiproliferative effects on tumor cells (Kwon et al., 2003). On the other hand, in the case of *Angelica sinensis* (Oliv.) Diels

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**TABLE 8 | Potential mechanism of core herbs included in this review**

| First author (Year) | Scientific name of herbal materials | Possible active ingredients | Target cell line or animal model | Possible mechanisms |
|---------------------|-------------------------------------|-----------------------------|---------------------------------|---------------------|
| Kwon et al. (2003)  | *Prunus persica* (L.) Batsch [Rosaceae], *Prunus persica* (L.) Batsch [Rosaceae] | Amygdalin (active D-form) | Human promyelocytic leukemia (HL-60) cells | Antiproliferative effect: cytotoxic to HL-60 cells with IC50 of 6.4 mg/ml in the presence of 250 nM of beta-glucosidase as induced nuclear morphology changes and internucleosomal DNA fragmentation |
| Chiu et al. (2017)  | *Angelica sinensis* (Oliv.) Diels [Apiaceae], *Angelica sinensis* (Oliv.) Diels [Apiaceae] | N-butylideneephthalide | Human bladder cancer cell lines TCCSUP, 5637, T24, and BFTC (BFTC 905) | Antiproliferative effect: bladder cancer cell death in a time- and dose-dependent manner and induced apoptosis via the activation of caspase-9 and caspase-3, migration of bladder cancer cells suppression, upregulation of E-cadherin and downregulation of N-cadherin, suppressed BFTC xenograft tumor growth |
| Zhang et al. (2019) | *Carthamus tinctorius* L. [Asteraceae], *Carthamus tinctorius* L. [Asteraceae] | Hydroxysafflor yellow A | H22 tumor-bearing mice HepG2 cells | Anti-angiogenic effect: MMP-2 and MMP-9 decrease in H22-transplanted tumor tissue, COX-2 expression was reduced via p38MAPK|ATF-2 signaling pathway, suppression of p38 activation by SB203580 decreased the HepG2 cell viability, proliferation, and migration |
| Zhang et al. (2016) | *Paeonia lactiflora Pall.* [Paeoniaceae], *Paeonia lactiflora Pall.* [Paeoniaceae] | Paeoniflorin | Human breast cancer cell lines (MDA-MB-231 and MCF-7) | Antiproliferative effect: inhibits the proliferation and invasion of breast cancer cells through suppressing the Notch-1 signaling pathway |
| Sheu et al. (2015)  | *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae], *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae] | Harpagoside | Microglia cells harvested from neonatal IOR mice were activated by exposure to hypoxia | Antiproliferative effect: scavenges hypoxia-enhanced inflammatory genes expression (COX-2, IL-1β and IL-6 genes) and NO synthesis of microglial cells through the NF-κB signaling pathway |
| Wang S. J. et al. (2013) | *Glycyrrhiza uralensis* Fisch. ex DC. [Fabaceae], *Glycyrrhiza uralensis* Fisch. ex DC. [Fabaceae] | Isoliquiritigenin | Human umbilical vein endothelial cells (HUVECs) | Anti-angiogenic effect: inhibit VEGF expression in breast cancer cells via promoting HIF-1α proteasome degradation, suppressed VEGF/VEGFR signaling pathway |

**ATF-2, activating transcription factor 2; BFTC, bladder transitional cell carcinoma; COX-2, cyclooxygenase 2; EPK, extracellular-signal-regulated kinase; HIF-1α, hypoxia-inducible factor-1α; HL, human leukemia; IC50, inhibitory concentration 50; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.**

**Prunus persica** L. [Asteraceae] - *Prunus persica* (L.) Batsch [Rosaceae], and *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae] - *Paeonia lactiflora* Pall. [Paeoniaceae], could also be predicted to have these benefits. For example, in 2012, it was reported that the major volatile component identified in the *Carthamus tinctorius* L. [Asteraceae] - *Prunus persica* (L.) Batsch [Rosaceae] extract combination in hot water was completely different from that of each single herb (Fu et al., 2012). Based on these results, the authors explained that the pharmacologically active compounds of the two-herb pairs recipe might be different from those of the single herbs which make them up. Data from another study examining the effects of *Carthamus tinctorius* L. [Asteraceae] - *Prunus persica* (L.) Batsch [Rosaceae] combination revealed that the herb pair could control liver inflammation and fibrosis by inhibiting pathological angiogenesis and hepatic fibrosis (Xi et al., 2016). This can be regarded as an example of the individual pharmacological activities of *Carthamus tinctorius* L. [Asteraceae] and *Prunus persica* (L.) Batsch [Rosaceae] that are strengthened through the synergistic effect of the mechanism discussed above. However, association rule mining is literally just a search tool for core patterns and cannot prove a causal relationship (Agrawal et al., 1993). Therefore, the herbal combination patterns identified in this review can be meaningful at the level of a valuable research hypothesis that needs to be verified through follow-up studies on whether they actually have amplified synergistic effects on cancer pain.
[Apiaceae], Paeonia lactiflora Pall. [Paeoniaceae], and Scrophularia ningpoensis Hems.
[Scrrophulariaceae], similar effects have been reported based on the action of each active ingredient, such as
N-butylidenephthalide, paoniflorin, and harpagoside (Sheu et al.,
2015; Zhang et al., 2016; Chiu et al., 2017). In the case of
Carthamus tinctorius L. [ Asteraceae] - Prunus persica (L.) Batsch [Rosaceae] and
Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae], anti-angiogenic
effects were also related to the respective active ingredients
hydroxysafflor yellow A and isoliquiritigenin (Wang Z. et al., 2013;
Zhang et al., 2019). As previously discussed, it can be estimated that
the action of EAHM at the individual component level and the
synergistic effect through the complex action were combined to affect
cancer pain caused by various pathologies and causes. It is reasonable
to assume that these may be related to the positive clinical outcomes
observed in this review. Therefore, it is worth specifically examining
which herb combination can be used more effectively and safely for
cancer pain compared to other individual herbs and herb pairs in
future research and drug development.

5 CONCLUSION

This systematic review supports that EAHM therapy can
minimize adverse events for upper and lower gastrointestinal
reactions, such as nausea and constipation. Moreover, this meta-analysis demonstrated that EAHM
combined with conventional medicine showed significantly
to better outcomes in response rate, continuous pain intensity,
total duration of pain relief, performance status, opioid usage,
and incidence of adverse events than prescribing conventional
medicine alone. Furthermore, EAHM-combined therapy and
monotherapy may result in a decrease in neurological side
effects, such as drowsiness and headache, when treating cancer
patients.

Considering the association rules on herb pairs, the four
combinations of herb pairs, which were Prunus persica (L.)
Batsch [Rosaceae] - Angelica sinensis (Oliv.) Diels [Apiaceae],
Prunus persica (L.) Batsch [Rosaceae] - Paeonia lactiflora Pall.
[Paeoniaceae], Carthamus tinctorius L. [Asteraceae] - Prunus persica
(L.) Batsch [Rosaceae], and Scrophularia ningpoensis Hems.
[Scrophulariaceae] - Paeonia lactiflora Pall. [Paeoniaceae],
have been widely used among cancer treatment-related herbs.
Besides, when one particular herb is employed to decrease cancer
pain, it is likely that another herb may be used. Hence, they may be
salutary for cancer patients to release cancer-related pain.

However, additionalRCTs with a more valid outcome
measure and an appropriate double-blind method should be
additionally performed to draw more firm conclusions.
Separately, it is considered worthwhile to conduct a follow-up
study to verify the specific target and clinical superiority of the
core herb combination pattern derived from this review.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in
the article/Supplementary Material; further inquiries can be
directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

H-GJ, JS, and DL were responsible for the conceptualization,
contributed to the methodology, and conducted the formal
analysis. H-GJ was responsible for the software and visualization.
H-GJ, JS, SC, and DL were responsible for the validation, conducted
the investigation, were responsible for the resources, and reviewed
and edited the manuscript. H-GJ, JS, and SC were responsible for the
data curation. H-GJ and JS prepared and wrote the original draft. DL
supervised the work and acquired the funding; H-GJ and DL were
responsible for the project administration.

FUNDING

This research was supported by the Bio & Medical Technology
Development Program of the National Research Foundation
(NRF), funded by the Ministry of Science & ICT
(2020M3A9E4104380).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at:
https://www.frontiersin.org/articles/10.3389/fphar.2021.800571/
full#supplementary-material

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