East Asian herbal medicine for cancer pain
A protocol for systematic review and meta-analysis with using association rule analysis to identify core herb pattern

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Abstract
Background: 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 is to systematically evaluate the efficacy and safety of oral administration East Asian herbal medicine (EAHM) for primary cancer pain, and to explore core herb patterns based on collected data.

Methods: A comprehensive literature search will be conducted in 10 electronic databases including 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), CiNii for randomized controlled trials from their inception until August 19, 2021. Statistical analysis will be performed in the software R version 4.1.1. and R studio program using the default settings of the ‘meta’ package. When heterogeneity in studies is detected, the cause will be identified through meta regression and subgroup analysis. Methodological quality will be assessed independently using the revised tool for risk of bias in randomized trials (Rob 2.0).

Results: This study will provide more comprehensive and specific evidence of EAHM for cancer pain management.

Conclusions: Based on the results of this review, it is expected that the efficacy and safety of East Asian herbal medicine for cancer pain may be confirmed. In addition, it will be possible to derivation of a core herb pattern related to this research topic through additional association rule mining analysis.

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, CIINAHL = Cumulative Index to Nursing & Allied Health Literature, CiNii = Citation Information by NII, CM = conventional medicine, CNKI = China National Knowledge Infrastructure, DPN = Diabetic peripheral neuropathy, EAHM = East Asian herbal medicine, EECM = East Asian herbal medicine combined conventional medicine, EMBASE = Excerpta Medica database, GRADE = grading quality of evidence and strength of recommendations in clinical practice guidelines, KCI = Korea Citation Index, KISS = Korean studies Information Service System, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, PROSPERO = International prospective register of systematic reviews, RCT = Randomized controlled trials, RISS = Research Information Service System, RoB = Risk of bias.

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

1. Introduction

Pain is an important factor influencing clinical outcome in the medical management of cancer. Recent literature on the prevalence of cancer pain reports that not only 60% of patients with advanced or metastatic cancer complain of pain, but also moderate to severe pain is observed in more than one-third of the patients.[1,2] Although clinicians’ awareness of cancer pain is gradually improving, there is still a report that about one-third of cancer survivors do not have access to proper management.[3] In addition to this, a significant number of patients still suffer from pain after completing curative treatment.[1] 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.[4] However, a large number of patients complain of severe pain that does not respond to treatment even after receiving opioids.[3] Meanwhile, concerns of medical consumers about opioids administration due to the continuous increase in accidental prescription opioid overdose or patients’ financial problems are also pointed out as important barriers.[5,6]
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 are being actively conducted recently.\(^8\) 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.\(^9\)-\(^12\) Recently, a number of clinical and experimental studies on various problems caused by cancer have been reported based on the scientific method-based approach to East Asian herbal medicine (EAHM).\(^13\)-\(^15\)

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. Systematic literature review on the efficacy and safety of overall oral EAHM focusing on improvement of pain intensity and response rate of cancer pain excluding secondary pain caused by anti-cancer treatment. Apriori algorithm-based association rule mining is performed on the herb data collected in this review to discover core herb pattern.

2. Methods

The present review will be conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 statement.\(^16\) The protocol of this systematic review was prepared according to preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015,\(^17\) and was pre-registered in PROSPERO (Registration Number: CRD42021265804). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021265804.

2.1. Search strategy

Randomized controlled trials (RCTs) that evaluated the efficacy of EAHM for cancer pain will be searched in the following 10 electronic databases from their inception until August 19, 2021: 4 English databases (PubMed, Cochrane Library, Cumulative Index to Nursing & Allied Health Literature, Excerpta Medica database), 4 Korean databases (Korean Studies Information Service System, Research Information Service System, Oriental Medical Advanced Searching Integrated System [OASIS], Korea Citation Index), 1 Chinese databases (Chinese National Knowledge Infrastructure Database), 1 Japanese database (Citation Information by NII). The following Boolean format will be used for the search: [Pain[MeSH] OR Pain*[TIAB] OR analgesia OR analges* OR nocicept* OR neuroarth*] 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]).

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 will be included. There will be no restrictions on language and publication time. Some studies will be excluded if they met the following criteria: not RCT or quasi RCT; the control group is not used or is inappropriate; unrelated to cancer pain; animal experiments; case reports or review; and not published in scientific peer-reviewed journals, including postgraduate theses or dissertations. A PRISMA 2020 flow chart will be produced to show the number of articles identified, screened, included, and excluded (shown in Fig. 1).

2.2.2. Type of participants. Trials will be considered eligible for inclusion if they were conducted in patients with cancer pain, with no restriction on age, sex, or race. However, studies in which patients’ secondary cancer related pain induced by other antitumor treatments such as chemotherapy or surgery were enrolled will be excluded because this review set primary cancer pain as the target disease.

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 will be included. RCTs that tested EAHM combined CM versus CM alone will be also considered. All forms of EAHM such as decoction, granule, capsule for the management of cancer pain will be included. There will be no restrictions on the dose and duration of treatment for EAHM, but the mode of delivery will be 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 will be excluded. Studies in which the comparators included other EAHMs will be excluded. In addition, studies that could not confirm the composition of individual ingredients and herbs of the utilized EAHM prescription will be also excluded.

2.2.4. Type of outcome measures. The primary outcome for cancer pain patients will be the response rate of remission for each group measured using the verbal rating scale (VRS), numerical rating scale (NRS), and visual analogue scale (VAS). In addition, individual continuous pain intensity outcomes such as NRS and VAS will be also adopted as primary outcomes. It will be used as a secondary outcome that closely reflects outcomes in patients with cancer pain, such as duration of pain relief, performance status, and opioid use. Meanwhile, to evaluate the safety of the intervention for cancer patients, the incidence of adverse events (AE) will also be included as a secondary endpoint.

2.2.5. Data extraction. Titles and abstracts of potentially eligible studies will be independently screened by 2 investigators according to the search strategy mentioned above. For the selected studies, 2 reviewers will independently collect the following information from the included studies: title, first author’s name, year of publication, sample size, age of participants, sex distribution, study design, cancer type, treatment and interventions for controls, duration of treatment, outcome measures, reported adverse events, and dosages of
EAHMs. Any discrepancies will be resolved through discussion among researchers.

2.2.6. Methodological quality assessment. The methodological quality of each included study will be independently evaluated by 2 investigators according to Rob 2.0, a modified tool for risk of bias (RoB) in randomized trials.[18] Rob 2.0 consists of 5 domains: bias arising from the randomization process, bias deviating from the intended intervention, bias due to omission of outcome data, and bias in the selection of reported outcomes. Methodological quality is “high risk of bias.” It will be assessed on 3 levels of “low risk of bias” and “some concerns,” and discrepancies between raters will be resolved through discussion.

2.2.7. Statistical analysis

2.2.7.1. Evidence synthesis. Evidence synthesis of included studies with available data will be performed by calculating the effect size and 95% CI using only the random effect model. Heterogeneity will be considered statistically significant when the $P$-value based on the chi-squared test is <.10 or $I^2$ is ≥50%. Two-sided $P < .05$ will be considered statistically significant. Statistical synthesis of individual research results will be performed in the software 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.[19] In this review, in order to effectively reveal the exact value of the effect size without relying only on the $P < .05$ significance threshold in the interpretation of the primary outcome synthesis result, a drapery plot will be additionally illustrated along with the forest plot.[20] Summary relative risk (RR) and 95% confidence interval (CI) will be calculated for response rate. Standardized mean difference (SMD) and 95% CIs will be calculated for continuous pain intensity and duration of pain relief. Mean difference (MD) and 95% CIs will be calculated for opioid usage and performance status. AEs will be calculated using the odds ratio because the probability of an event is significantly lower than that of other outcomes and it is necessary to estimate a causal relationship. The results of individual studies using outcomes for which synthesis is inadequate will be described in the text. If heterogeneity is detected in the synthesized results
through meta-analysis, meta regression analysis and subgroup analysis will be performed to determine the cause. In order to distinguish publication bias, a contour-enhanced funnel plot will be used for the outcome that included the most studies. \[21\] For the asymmetry on the visually confirmed funnel plot, Egger test\[22\] and Begg test\[23\] will be 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 will be explored. Before proceeding with this analysis, preliminary information for data mining will be 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) will be used for the Apriori association rule analysis and plot production. A data fit will be done by using “arules” package in R studio. \[24\] The function of the R package “arulesViz” will be applied to generate graphical presentations according to the results. \[25\] Mining of frequent hub item sets and association rules will be performed according to the Apriori algorithm method for discovering meaningful relationships between variables in a large database. \[26\] 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. \[27–29\]

In the Apriori algorithm, support, confidence, and lift are the main metrics for measuring association. A rule is defined as an expression $X \Rightarrow Y$ where $X$, $Y \subseteq I$ and $X \cap Y = \emptyset$. 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 which 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 $conf(X \Rightarrow Y) = \frac{supp(X \cup Y)}{supp(X)}$, measuring how likely it is to see herb $Y$ in a transaction containing herb $X$. An association rule $X \Rightarrow Y$ needs to satisfy $supp(X \cup Y) \geq \sigma$ and $conf(X \Rightarrow Y) \geq \delta$, where $\sigma$ and $\delta$ are the minimum support and minimum confidence, respectively. Confidence can be interpreted as an estimate of the probability $P(Y|X)$, the probability of finding the RHS of the rule in transactions under the condition these transactions also contain the LHS. Lift of a rule is defined as $lift(X \Rightarrow Y) = \left( \frac{supp(X \cup Y)}{supp(X)} \right)$. Support is a 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 correlation is interpreted as strong. In this review, the association rules will be identified based on the minimum values for support and confidence being 20% and 80%, respectively. And it will be deriving the core herb pattern and its constituent herbs that show the most obvious association among them.

2.2.8. Quality of evidence according to outcome measurements. The overall quality of evidence for each outcome will be evaluated according to the grading of recommendations assessment, development, and evaluation pro.\[30\] The grading quality of evidence and strength of recommendations in clinical practice guidelines assessment evaluates the overall quality of evidence in four levels: very low, low, moderate, and high. The level of evidence is lowered according to factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias, respectively.

3. Amendments

If there is a significant modification or change of this protocol, the details and date of all amendments will be described in the final report.

4. Ethics and dissemination

In the process of implementing this systematic review, personal information will not be disclosed or published. This review will not infringe the rights of the subjects. Since it is not a clinical study that directly recruited subjects, ethical approval is not possible. The results of this study will be reported in a peer-reviewed scientific journal.

5. Discussion

This systematic review will provide comprehensive information on the efficacy and safety of EAHM for cancer pain. Several systematic reviews have already been reported to investigate the palliative effects of herbal medicine for cancer pain.\[31–35\] 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, systematic reviews that reflect these results need to be continued. On the other hand, prior reviews for EAHM comprehensively deal with several types of EAHM formulas including multiple herbal ingredients, unlike reviews on CM with a single dose and composition. For this reason, it is difficult to identify which of the many herb-related information reflected in the review is useful information.

In such a situation, the evidence according to this review will provide more comprehensive and specific information to both clinicians who manage cancer pain. In addition, it is expected that the derivation of core herb pattern using data mining techniques can be used as a hypothesis worthy of follow-up research in the development of new drugs related to the subject.

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Author contributions

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References

[1] van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 2007; 18:1437–49.
[2] van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016;51:1070.e9–90.e9.
[3] Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol 2014;32:4149–54.
[4] Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician Med Fam Can 2010;56:514–7, e202–e205.
[5] Anderson KO, Mendoza TR, Valero V, et al. Minority cancer patients and their providers: pain management attitudes and practice. Cancer 2000;88:1929–38.
[6] Calcaterra S, Glanz J, Binswanger IA. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. Drug Alcohol Depend 2013;131:263–70.
[7] Kwon J-H. Overcoming barriers in cancer pain management. J Clin Oncol 2014;32:1727–33.
[8] Deng G. Integrative medicine therapies for pain management in cancer patients. Cancer J Sudbury Mass 2019;25:343–8.
[9] Chen H-Y, Lin Y-H, Su IH, Chen Y-C, Yang S-H, Chen J-L. Investigation on Chinese herbal medicine for primary dysmenorrhea: implication from a nationwide prescription database in Taiwan. Complement Ther Med 2014;22:116–25.
[10] Lin P-H, Lin S-K, Hsu R-J, Cheng K-C, Liu J-M. The Use and the prescription pattern of traditional chinese medicine among urolithiasis patients in Taiwan: a population-based study. J Altern Complement Med 2016;22:88–95.
[11] Arai Y-C, Makino I, Ikemoto T, Terajima Y, Owari K. Kampo for the treatment of pain in japan: a review. Pain Ther 2020;9:161–70.
[12] Wang C, Meng Q. Global research trends of herbal medicine for pain in three decades (1990–2019): a bibliometric analysis. J Pain Res 2021;14:1611–26.
[13] Lin T-H, Chen S-I, Su Y-C, Lin M-C, Lin H-J, Huang S-T. Conventional Western treatment combined with chinese herbal medicine alleviates the progressive risk of lung cancer in patients with chronic obstructive pulmonary disease: a nationwide retrospective cohort study. Front Pharmacol 2019;10:9877.
[14] Tsai F-J, Liu X, Chen C-J, et al. Chinese herbal medicine therapy and the risk of overall mortality for patients with liver cancer who underwent surgical resection in Taiwan. Complement Ther Med 2019;47:102213.
[15] Kim D, Park M, Haleem I, et al. Natural product Ginsenoside 20(S)-25-triol in cancer treatment: a review of the pharmacological mechanisms and pharmacokinetics. Front Pharmacol 2020;11:521.
[16] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71.
[17] Shamsi S, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P): 2015: elaboration and explanation. BMJ 2015;350:g7647.
[18] Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:14898.