

# Herbal Medicine for Liver Cancer: A Protocol for Systematic Review and Meta-Analysis

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### ABSTRACT

**Introduction:** The aim of this systematic review is to provide evidence confirming the efficacy and safety of herbal medicines used in the treatment of liver cancer.

**Methods:** The review will include randomized clinical trials that compared herbal medicines used as treatments for liver cancer with other therapies, such as placebos and Western medicine. Only randomized controlled trials will be included in this review, and all types of herbal medicine will be evaluated. Eleven electronic databases will be searched from the inception date: the Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, AMED, CINAHL, one Chinese database (CNKI), and five Korean databases (OASIS, DBpia, RISS, KISS, and NDSL). The selection of studies, data extraction, and management will be performed independently by four researchers. Methodological quality, including the risk of bias, will be assessed using the Cochrane risk-of-bias assessment tool.

**Results:** The review of current evidence for the effectiveness of herbal medicine for liver cancer will be summarized and quantitatively analyzed.

**Conclusions:** Our systematic review will provide evidence of the efficacy of herbal medicines as treatments for liver cancer. This evidence will provide useful information for practitioners and patients in the fields of oncology and complementary medicine.

**Systematic review registration:** 2021 CRD42021268386

**Key words:** liver cancer, hepatic cancer, herbal medicine, systematic review, protocol

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## I . Introduction

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Liver cancer is a malignant tumor that begins in the liver cells. Liver cancer is also known as hepatic cancer, primary hepatic cancer, or primary hepatic malignancy. Secondary liver cancer is

cancer that metastasizes to the liver from outside the liver<sup>1</sup>. Secondary liver cancer is much more common in North America and Europe, whereas primary liver cancer is more common in Southeast Asia<sup>2</sup>. Various risk factors for liver cancer, including chronic hepatitis B and hepatitis C, alcohol, metabolic liver disease such as nonalcoholic fatty liver disease, and exposure to dietary toxins, have been reported<sup>3</sup>.

Liver cancer is the 6th most commonly diagnosed cancer and the 4th leading cause of cancer-related death worldwide<sup>4</sup>. Whereas disease burdens and impacts of many other major cancers are decreased, the overall burden of liver cancer increases over time. Liver cancer is the second leading cause of years of life lost from cancer worldwide, with a 4.6% increase in the absolute years of life lost<sup>3</sup>.

Treatment options for liver cancer depend on various factors, such as the complex interplay between tumor stage and the extent of underlying liver diseases, as well as the patients' general health status. Treatment for advanced disease includes surgical treatment, liver transplantation, local ablation, transarterial chemoembolization, radiation therapy, and systemic treatment such as standard frontline therapy, cytotoxic chemotherapy, and immunotherapy<sup>5</sup>.

However, surgical resection, chemotherapy, and radiation therapy can cause adverse effects and complications. Moreover, the recurrence rate of liver cancer after treatment is high because patients often have underlying liver diseases that influence the recovery of liver function.

Herbal medicine is a complex extract with a multi-target approach for treatment. In addition, herbal medicine is applied by dividing a patient's constitution or symptoms using a holistic approach.

Therefore, herbal medicines for liver cancer are used in various ways depending on the type and stage of liver cancer. Combined treatment with herbal medicine and conventional treatment might postpone tumor recurrence and metastasis and prolong the overall survival of patients with primary hepatic carcinoma. It is also reported to improve short-term clinical efficacy and quality of life, even with fewer adverse effects<sup>6</sup>. It has been reported that herbal medicines containing ginseng, astragalus, and mylabris have a larger treatment effect<sup>7</sup>.

In this study, any type and clinical stage of liver cancer and any type and form of herbal extract will be included. Furthermore, we will analyze the subgroups according to the type of subject and intervention and analyze the constituents and ingredients of the herbal medicine. We will also include additional studies since the last study. Hence, this study aims to evaluate the efficacy and safety of herbal medicines in the treatment of liver cancer.

## II . Materials and Methods

### 1. Study registration

The protocol of this systematic review was registered in PROSPERO 2021 (registration number: CRD42021268386).

### 2. Inclusion criteria for study selection

#### 1) Type of studies

Only randomized controlled trials of herbal medicine for liver cancer will be included in the review. Non-randomized clinical, observational, case, qualitative, and laboratory studies will be excluded. Trials that fail to provide detailed results will also be excluded. We will include peer-reviewed publications

in English, Chinese, and Korean languages.

2) Type of participants

Patients diagnosed with liver cancer will be included regardless of their age, sex, race, duration, type, and clinical stage of liver cancer.

3) Types of interventions and controls

We will include patients treated with herbal medicine alone or with herbal medicine in addition to other cancer treatments. Any formulation (e.g., decoctions, tablets, capsules, extracts, powders, pills, injections) of herbal medicine will be eligible for inclusion. Studies that do not list the composition of the herbal medicines used unless patented will be excluded.

Interventions in the control group will include no intervention, placebo, or any type of control intervention.

4) Type of outcome measures

Primary outcomes:

Overall survival and progression-free survival.

Secondary outcomes:

(1) Overall response rate (ORR) and disease control rate (DCR): ORR is the rate of partial or complete response to treatment, and DCR is the rate of tumorigenic effects in a stable disease state.

(2) The frequency, severity, or scale of cancer-related symptoms.

(3) Quality of life (e.g., Karnofsky performance score [KPS] and quality of life improved rate [QIR]).

(4) Number and severity of adverse events.

3. Data sources

The following 11 electronic databases will be searched from inception to December 2021: the Cochrane Database of Systematic Reviews, MEDLINE, Excerpta Medica dataBASE (EMBASE), Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), one Chinese database (China Academic Journals full-text database [CNKI]), and five Korean databases (Online Acquisitions and Selection Information System [OASIS], DBpia, Research Information Service System [RISS], Korean Information Service System [KISS], and National Discovery for Science Leaders [NDSL]). The reference lists of eligible studies were manually searched to identify potential articles.

4. Search strategy

Our search strategy will include the keywords “herbal medicine” and “liver cancer.” The search strategy for MEDLINE is shown in Table 1. The search words used in the Chinese and Korean databases have the same meanings as those used in the English databases.

Table 1. Search Strategy Used in MEDLINE Database

Number	Search terms
1	"Clinical Trials as Topic" [Mesh]
2	randomized controlled trial [pt]
3	controlled clinical trial [pt]
4	randomized controlled trial [mesh]
5	randomized allocation [mesh]
6	randomized [tiab]
7	randomised [tiab]
8	placebo [tiab]
9	randomly [tiab]
10	trial [tiab]
11	or 1 - 10
12	animals [mesh] NOT humans [mesh]
13	11 NOT 12
14	Hepatocellular Carcinoma* [tiab]
15	Liver Cell Carcinoma* [tiab]
16	Liver Cancer* [tiab]
17	Hepatoma* [tiab]
18	Hepatic Carcinoma* [tiab]
19	Hepatic Cell Carcinoma* [tiab]
20	Hepatocarcinoma* [tiab]
21	Liver Carcinoma* [tiab]
22	Malignant Hepatoma* [tiab]
23	or 14 - 22
24	herbal med* [tiab] or herbal com* [tiab] or herb* [tiab]
25	traditional kor* [tiab] or korean med* [tiab]
26	traditional chin* [tiab]
27	kanpo [tiab] or kampo [tiab]
28	decoction [tiab]
29	or 24 - 28
30	13 and 23 and 29

This search strategy will be modified as required for other electronic databases.

## 5. Data collection and analysis

### 1) Study selection

Two authors (SK, and GS) will independently screen the titles and abstracts of eligible studies. Disagreements will be resolved through discussions between all authors. When disagreements on the

selection cannot be resolved through discussion, the arbiter (SY) will make a final decision. Details on study selection will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1).

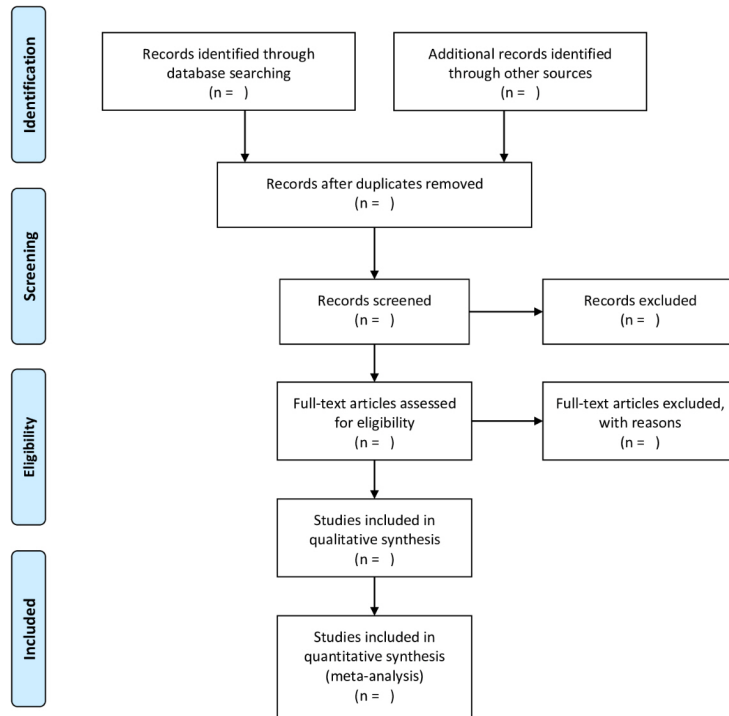


Fig. 1. Study selection flow diagram.

## 2) Data extraction and management

Data extraction and quality assessment will be conducted independently by all the authors. The extracted data will be written in a standard form (e.g., authors, study design, participants, control, intervention, outcome measures, and results). The participants' information will include age, sex, duration, type, and clinical stage of liver cancer. If there is a disagreement between the authors regarding the extracted data, a consensus will be reached at a meeting between all authors. If there is insufficient data, SY will contact the original study author via email to request additional information.

## 3) Assessment of risk of bias in the included studies

All reviewers will assess the risk of bias (RoB)

based on the Cochrane Handbook<sup>8</sup>. The following domains will be assessed: sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting. The assessment results will be presented as follows: low, unclear, and high RoB according to the Cochrane guidelines. If there are any differences in opinion between the authors, a consensus will be reached at a meeting between all authors.

## 4) Measures of the treatment effect

For continuous data, the pooled results will be presented as the mean difference (MD) or standardized MD with 95% confidence intervals (CIs). For dichotomous data, the risk ratio (RR) with 95% CIs will be used to measure the treatment

effect.

5) Dealing with missing data

In studies with missing data, we will contact the corresponding author of the original article to request this data. If information cannot be obtained, we will analyze only the available data.

6) Assessment of heterogeneity

We will use fixed-effects and random-effects models for the meta-analysis according to the data analysis. The  $I^2$  test will be used to test statistical heterogeneity, using 50% as the cutoff point for meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis to explore the possible causes.<sup>8</sup>

7) Assessment of reporting bias

Funnel plots will be used to detect reporting biases, and Egger's regression test will be used to determine funnel plot asymmetry when more than ten studies are available<sup>8,9</sup>.

8) Data synthesis

Meta-analysis will be performed to assess the differences between the intervention and control groups using Review Manager software (RevMan, V.5.4 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark). RR and 95% CIs will be assessed for the effect size of each included study. A fixed-effects model will be used for pooled data if no substantial statistical heterogeneity is detected. Otherwise, a random-effects model will be used. The studies will be synthesized according to the type of intervention and/or control as follows:

- (1) Herbal medicine vs. conventional Western medicine (only medication)
- (2) Herbal medicine vs. placebo
- (3) Herbal medicine+conventional Western medicine vs. placebo+conventional Western medicine
- (4) Herbal medicine+conventional Western medicine

vs. conventional Western medicine

9) Subgroup analysis and investigation of heterogeneity

When sufficient studies are available, subgroup analyses will be conducted on the following topics:

- (1) Type of clinical stage of liver cancer
- (2) Type of conventional treatment (e.g., transcatheter arterial chemoembolization, chemotherapy, radiotherapy, surgery)
- (3) Type of herbal medicine (e.g., decoctions, tablets, capsules, extracts, powders, pills, injections)
- (4) Type of control (e.g., no treatment, placebo, Western medicine)

We will check the heterogeneity of participants' demographic characteristics, liver cancer stage, and herbal medicine prescription (type, administration method, administration period, etc.), and studies with too much heterogeneity will be excluded at the discretion of the investigator.

10) Sensitivity analysis

Sensitivity analysis will be conducted to identify the stability and robustness of the study results by removing poor-quality studies, missing values, and outliers.

11) Quality of evidence

The Grading of Recommendations Assessment Development and Evaluation (GRADE) approach will be used to evaluate the quality of evidence for each outcome. The quality of evidence will be categorized into four levels: high, moderate, low, and very low.

12) Ethical approval

Formal ethical approval is not necessary because this study will be based on published research.

### III. Discussion

Herbal medicine has been widely used to treat patients with liver cancer in Asia, and it might be a good therapeutic option for patients. Herbal medicine can be used in various ways, depending on the clinical stage, severity, and complaints of liver cancer.

In this study, we will include patients diagnosed with liver cancer, regardless of their age, sex, race, duration, type, and clinical stage of liver cancer. All types of herbal medicine will be included.

Several indicators can be used to evaluate the effects of cancer treatment, and we will analyze overall survival and progression-free survival as the primary outcomes. Secondary outcome measures will also be analyzed, including ORR, DCR, frequency, severity, or scale of cancer-related symptoms, quality of life, and the number and severity of adverse events.

This systematic review will provide evidence of the efficacy and safety of herbal medicines in the treatment of liver cancer. This evidence will provide useful information to practitioners and patients in the fields of oncology and complementary medicine.

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### Author Contributions

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Funding acquisition: Seung-Bo Yang

Investigation: Seung-Bo Yang, Seungwon Kwon, Ga Yeon Song

Methodology: Seung-Bo Yang, Seungwon Kwon

Supervision: Seung-Bo Yang

Validation: Seung-Bo Yang, Seungwon Kwon, Ga Yeon Song

Writing - original draft: Seungwon Kwon

Writing - review & editing: Seung-Bo Yang

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## 간암에 대한 한약치료: 체계적 문헌고찰 및 메타분석의 프로토콜

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### 초 록

**서론:** 본 체계적 문헌 고찰의 프로토콜 논문은 간암의 한약 치료에 대한 효과와 안전성의 근거를 제시하는 것을 목표로 한다.

**방법:** 본 체계적 문헌 고찰은 간암에 한약 치료에 대한 무작위 대조 임상시험을 포함할 것이다. 오직 무작위 대조 임상시험 유형의 임상 연구만 포함할 것이다. 시험군의 한약 치료는 한약을 사용한 모든 제형을 포함할 것이며, 대조군은 다른 치료, 플라시보 치료, 서양의학적 치료 등을 포함할 것이다. 다음 11개의 데이터베이스를 활용하여 검색할 것이다: the Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, AMED, CINAHL, Chinese database(CNKI), 그리고 다섯 개의 한국 데이터베이스(OASIS, DBpia, RISS, KISS, and NDSL). 연구의 선정, 데이터 추출 및 분석 등의 업무는 3명의 연구자가 독립적으로 수행할 것이다. 비뮌 위험 평가를 포함한 연구의 질적 평가는 Cochrane risk-of-bias assessment tool을 사용할 것이다.

**결과:** 본 간암에 대한 한약 치료의 체계적 문헌 고찰은 최신의 근거를 요약적이고 분석적으로 제공할 것이다.

**결론:** 간암의 한약 치료에 대한 효과와 안전성의 근거를 제시할 것이며, 이는 종양학이나 한의학과 보완·대체의료 분야의 종사자들에게 유용한 정보를 제공할 것이다.

**체계적 문헌고찰 등록:** 2021 CRD42021268386

**중심어:** 간암, 간세포암종, 한약, 체계적 문헌고찰, 프로토콜

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