대한한방내과학회지 제45권 3호(2024년 6월)
J. Int. Korean Med. 2024;45(3):335-341
http://dx.doi.org/10.22246/jikm.2024.45.3.335

Herbal Medicines for the Improvement of Immune Function in Patients with Cancer: A Protocol for Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: Patients with cancer eventually fail to respond to therapy when malignant cells develop effective ways to evade immunosurveillance. Conventional cancer treatments, such as radiation therapy and chemotherapy, aim to cure the disease or prolong the patient's life. However, the toxicity and side effects of conventional treatments limit their efficacy. Herbal medicine is a typical complementary and integrative form of medicine for cancer treatment in Asia. This protocol evaluates the effectiveness of herbal medicines in improving the immune function of patients with cancer.

Methods: The following electronic databases will be searched: MEDLINE via PubMed, EMBASE via Elsevier, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), and Korean databases including Regional Information Sharing Systems (RISS), National Digital Science Library (NDSL), and Oriental Medicine Advanced Searching Integrated System (OASIS). Additionally, prospective randomized controlled trials that evaluate the effectiveness of herbal medicines on immune function in patients with cancer will be included in this review. All outcomes related to the immune function of patients with cancer (e.g., CD3, CD4, CD8, CD4/CD8 ratio, CD19 (B cells), dendritic cells (CD11), CD56 (NK cells), and macrophages) will be included in this review.

Results: This review is expected to provide data on the effectiveness of herbal medicines on improving immune functions in patients with cancers.

Conclusion: This systematic review will help patients and clinicians establish new management options for cancer treatment.

Key words: herbal medicine, immune function, cancer, patients with cancer, protocol

· 투고일: 2024.04.19, 심사일: 2024.06.25, 게재확정일: 2024.06.25
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Ⅰ. Introduction

The International Agency for Research on Cancer estimates that the global cancer burden rose to 19.3 million cases in 2020[1] and suggests that more than 50 million people are living with cancer diagnosed within the last five years. The

prevention and treatment of cancer is a significant public health challenge of the 21st century[2]. To reduce the overall mortality rate associated with cancer, combined success in cancer prevention, early detection, screening, and treatment is needed[3].

Conventional cancer treatments, such as radiation therapy and chemotherapy, aim to cure the disease or prolong the patient's life[4]. Nevertheless, they often lead to poor quality of life and dose delays because of their side effects and toxicities. Cytotoxic chemotherapy suppresses the hematopoietic system and increases the risk of life-threatening infections owing to neutropenia[5].

Cancer immunotherapy has been a paradigm in modern oncology since 1985. The mechanism of action of this therapy blocks the way cancer cells develop and evade immunosurveillance[6]. However, the response rates to immunotherapy vary widely among different cancers. Approximately 15-30% of patients respond objectively to immune checkpoint inhibitors[7].

Herbal medicine is a typical complementary and integrative medicine used in Asia to treat cancer[4]. Clinical trials using herbal medicines as adjuvant cancer treatments have shown effectiveness in reducing cancer-related fatigue, pain, and gastrointestinal side effects, such as vomiting, diarrhea, and nausea. A previous review showed that herbal medicine reduces respiratory tract infections, one of the most common complications of radiotherapy, and improves the symptoms of cachexia and quality of life in patients with cancer[8].

In many pre-clinical studies, herbal medicine has demonstrated antitumor effects by upregulating immune responses in the immunosuppressive tumor microenvironment (TME)[9]. Furthermore, a clinical trial using herbal extracts evaluated changes in NK cell activity. The herbal intervention group had a higher immunoregulatory effect than the placebo group[10].

Even so, clinical trials using herbal medicines to improve immune function in patients with cancer have yet to be systematically examined. Our study will review randomized controlled trials (RCTs) that evaluate the effectiveness of herbal medicines in improving immune function in patients with cancer[4].

Ⅱ. Methods

1. Study registration

This review's protocol was registered in PROSPERO (registration number CRD42022354649).

We will conduct a systematic review according to this protocol, and the dates, changes, and rationales for each amendment will be tracked in PROSPERO if no protocol amendments are made. This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline[11].

2. Search method for identifying the studies

The following electronic databases will be searched: MEDLINE via PubMed, EMBASE via Elsevier, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), and Korean databases, including Regional Information Sharing Systems (RISS), National Digital Science Library (NDSL), and Oriental Medicine Advanced Searching Integrated System(OASIS). The reference lists of the retrieved articles will be manually searched, and previous review articles will be examined. There will be no restrictions on

the year or language of the reviewed publications.

The search strategy for Medline is shown in Table 1 and will be modified similarly for other databases.

Table 1. Medline Search Strategy

	Searches
#1	"cancer" [TIAB] OR "carcinoma" [MH] OR "carcinoma"[TIAB] OR "tumor"[TIAB]
#2	"Herbal Medicine" [MH] OR "Prescription Drugs" [MH] OR "Plants, Medicinal"[MH] OR "Drugs, Chinese Herbal"[MH] OR "Medicine, Chinese Traditional"[MH] OR "Medicine, Kampo" [MH] OR "Medicine, Korean Traditional" [MH] OR "traditional Korean medicine"[TIAB] OR "traditional Chinese medicine"[TIAB] OR "traditional oriental medicine" [TIAB] OR "Kampo medicine" [TIAB] OR herb*[TIAB] OR decoction*[TIAB] OR botanic*[TIAB] OR "Chinese patent medicine"[TIAB]
#3	Randomized Controlled Trial" [PT] OR "Controlled Clinical Trial" [PT] OR randomized[TIAB] OR placebo[TIAB] OR "Clinical Trials as Topic"[Mesh: noexp] OR randomly[TIAB] OR trial[TI]
#4	animals [MH] NOT humans [MH]
#5	(#1 AND #2 AND #3) NOT #4

3. Inclusion criteria for this review

1) Types of studies

This systematic review will include prospective RCTs. These RCTs will evaluate the effectiveness of herbal medicines on immune functions in patients with cancer. Studies with other designs, such as observational studies, cohort studies, case reports, case series, non-RCTs, and animal and experimental studies, will be excluded.

2) Types of participants

Patients with all types of cancer, regardless of sex, age, and cancer stage, will be included in the review.

3) Types of interventions

Studies including orally (e.g., decoction, tablets, pills, or powders) administered herbal medicines will be included in this review. RCTs in which other interventions (e.g., chemotherapy, radiation, and hormone therapy) were administered to all groups using same protocol will be included. The exclusion criteria include studies involving herbal extracts, herbal injections, and RCTs in which herbal medicines were combined with other interventions.

There will be no restrictions on comparisons. Placebos, active control groups, no-treatment groups, and wait-list control groups will be used as control groups.

4) Type of outcome measures

All outcomes related to immune functions of cancers (e.g., CD3, CD4, CD8, CD4/CD8 ratio, CD19 (B cells), dendritic cells (CD11), CD56 (NK cells), and macrophages) will be included in this review. However, RCTs that did not report the measured values before and after treatment will be excluded.

4. Data collection, extraction, and assessment

1) Selection of studies

Two authors (YC and SJ) will independently screen the titles and abstracts of studies retrieved from the databases after excluding duplicate articles. The full texts of the selected articles will

then be reviewed to ensure that each article meets the inclusion criteria for this review. Finally, a third reviewer (M-KJ) will provide the decisive factor if the two authors have a difference of opinion.

2) Data extraction

Two authors (YC and SJ) will extract the data, and a third author (M-KJ) will review the extracted data. Essential information for each article will be summarized, including the title, first author, published year, journal, study period, participants, interventions, comparisons, outcomes, results, and adverse events.

3) Assessment of risk of bias

Two reviewers (YC and SJ) will assess the quality of the included studies using the Cochrane Handbook risk of bias (RoB) assessment tool version 6.3[12]. RoB will be assessed using the following seven items: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) completeness of outcome data, 6) completeness of reporting, and 7) other sources of bias. In each RCT, items will be categorized as "high risk (H)," "unclear (U)," or "low risk (L)." In addition, an RoB graph will be generated using Review Manager (Cochrane Collaboration Software, RevMan), version 5.3 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012).

5. Data synthesis

Differences between the intervention and control groups will be assessed. The mean differences (MDs) with 95% confidence intervals (CIs) will be used to measure the treatment effects for continuous data. In addition, we will convert other forms of data into MDs. For outcome variables on different scales, standard MDs (SMDs) with 95% CIs will be used. For dichotomous data, we will present treatment effects as relative risks (RRs) with 95% CIs; other binary data will be converted into RRs.

All statistical analyses will be conducted using RevMan version 5.3. We will contact the corresponding authors of studies with missing information to acquire and verify the data whenever possible. We will pool the data across studies to conduct a meta-analysis using fixed or random effects. Finally, we will use the GRADEpro software from Cochrane Systematic Reviews to create a summary of the findings.

6. Ethical statement and Competing interests

All data in this study will be collected from published trials; therefore, ethical approval is not necessary. The authors declare no conflicts of interest.

Ⅲ. Results

This review is expected to provide data on the effectiveness of herbal medicines on improving immune functions in patients with cancers.

Ⅳ. Discussion

One in five individuals worldwide develops cancer during their lifetime. One in eight males and one in eleven females will die from the disease. Effective strategies to treat cancer still need to be improved[2]. Various studies have suggested that herbal medicine is an effective complementary medicine that reduces the side effects of conventional cancer treatments[13].

Herbal medicine can also be used to improve cancer-related fatigue, the most common symptom that affects the quality of life in patients with cancer[14]. Herbal medicine may work as an anti-cancer agent by exhibiting an anti-inflammatory and cytotoxic effect in tumors and by regulating the TME[15]. These mechanisms of action demonstrate the potential of herbal medicine to mitigate the limitations associated with conventional treatment methods[4].

A previous review showed that herbal medicine regulates both innate and adaptive immunity[9]. Herbal medicine achieves this regulation by promoting the quantity of components involved in innate immunity and phagocytic capacity and the maturation and expression of antibodies in acquired immunity[16].

Recent cancer immunotherapy targets the reactivation of the immune system by inhibiting tumor cell immune checkpoints. Understanding the interactions between tumor cells and immunomodulators in TME is needed to improve the reaction rate of cancer immunotherapy[17]. Herbal medicine is trend based on its multitarget compounds and antitumor effects on TME[18]. The clinical application of herbal medicines to improve immune function in the treatment of various cancer types is crucial. Eliminating cancer relies on restoration of the patient's immune function. This systematic review will help patients and clinicians establish new management options for cancer treatment.

Author contributions

Conceptualization : M-KJ, SJ
Methodology : SJ, MMK, M-KJ
Supervision : M-KJ, SJ
Writing-original draft : YC, SJ, HEJ
Writing-review & editing : M-KJ, HSY

Acknowledgments (Funding)

This study was supported by the Korea Institute of Oriental Medicine, Republic of Korea (KSN2022240), and the Korea Health Industry Development Institute (KHIDI), Republic of Korea (HF20C0038). The funding source will have no input for interpretation or publication of the study results.

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한약의 암 환자에 대한 면역기능 개선 효과 : 체계적 문헌고찰과 메타분석 프로토콜

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초 록

목적: 암 환자 치료에 대한 반응률은 종양 세포가 면역 회피 반응을 일으키면서 떨어지게 된다. 방사선 치료나 항암 치료 같은 표준 치료들은 병을 고치거나 환자들의 생명을 연장하는 목적으로 쓰이나 그 독성이나 부작용으로 인해 효과가 제한되고 있다. 한약은 아시아 지역에서 활용되고 있는 대표적인 보완 의학이며 면역 작용을 증강시키기 위해 널리 사용되고 있다. 이 프로토콜은 향후 암 환자들의 면역 기능을 개선시키는 데 있어서 한약의 객관적인 유효성을 체계적 문헌 고찰로 평가하고자 한다.

방법: 검색할 데이터베이스는 다음과 같다: MEDLINE via PubMed, EMBASE via Elsevier, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure(CNKI), Korean databases including Regional Information Sharing Systems(RISS), National Digital Science Library(NDSL), Oriental Medicine Advanced Searching Integrated System(OASIS). 한약을 이용해 암 환자들의 면역 기능 개선을 다룬 전향적 무작위 대조 연구들을 포함시키고, 면역 기능과 관련된 모든 지표들(CD3, CD4, CD8, CD4/CD8 비율, CD19(B세포), CD11(수지상세포), CD56(NK세포), 대식세포 등)을 분석한다.

결과: 암 환자의 면역 기능과 관련된 지표들을 포함시켜 체계적 문헌 고찰과 메타 분석을 수행할 예정이다.

결론: 한약의 암 환자 면역 기능 개선 유효성을 객관적으로 알리고, 본 연구를 통해 환자와 의료진에게 암 치료에 있어서 새로운 선택지를 넓힐 수 있도록 방향을 제시하고자 한다.

중심어: 한약, 면역 기능, 암, 암 환자, 프로토콜