대한한의학 방제학회지 제30권 제4호
Herbal Formula Science
2022;30(4):241~248.
pISSN 1229-1218, eISSN 2288-5641
https://doi.org/10.14374/HFS.2022.30.4.241
Official Journal of The Korean Medicine Society For The Herbal Formula Study
Available at http://www.formulastudy.com HFS

Original Article / 원저

배암차즈기의 투여가 고형암환자에 미치는 영향을 평가하기 위한 선행적 인체적용시험

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Effect of *Salvia plebeia* Extract on Patients with Solid Cancer: A Preliminary Clinical Trial Protocol

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ABSTRACT

Objective : The purpose of this trial is to observe the preliminary effects of *Salvia plebeia* (SP) extract on quality of life in patients with solid cancer.

Methods : This is a prospective, open-label, single-arm, and single-dose clinical trial. Twenty participants who have been diagnosed with solid cancer between the ages of 20 and 65 will be included. All participants will be administered SP granules for 12 weeks. Data will be collected at 4, 8, and 12 weeks after enrollment. The primary outcome is quality of life, using the Korean version of the Functional Assessment Cancer Therapy-General

questionnaire. Secondary outcomes include tumor markers in blood tests for each cancer type, soluble programmed death-ligand 1, the percentage of natural killer cells among lymphocytes, ratio of T-helper and T-suppressor cells, ratio of total T, T-helper, T-suppressor, and B cells in lymphocytes, level of C-reactive protein, and tumor size *via* radiology examination. Safety will be assessed by clinical laboratory tests and monitoring of adverse events.

Discussion : This study aims to observe the effects of an oral administration of SP preparations in patients with solid cancer on changes in quality of life and an improvement in immune function. It is expected to provide objective evidence of the effect and safety of SP for patients with solid cancer.

Trial registration: KCT0007315 (Clinical Research Information Service)

Key words : *Salvia plebeia* R. Br., Solid cancer, Herbal medicine, Clinical trial protocol.

1. Introduction

Salvia plebeia R. Br. (SP) is a traditional herbal remedy used in Korea to treat the common cold, flu, and cough[1]. It has also been used in other countries such as China, India, Japan, and Australia, and it was first documented in the *Compendium of Materia Medica* [2]. Recent studies have reported that SP has anti-inflammatory, antioxidative, antibacterial, and antiviral effects[3, 4]. The components of SP that perform these therapeutic effects have been analyzed; the results have shown phenolic substances, such as flavonoids, homoplantaginins, hispidulin, eupafolin, eupafolin-7-glucoside, refined components, and saponins[2]. Korean Patent Publication No. 2016-0146007 describes these components as an active ingredient for the prevention or treatment of respiratory inflammatory diseases[5].

Recently, combining natural products and chemotherapy in patients with tumors has improved the quality of life and reduced the side effects[6]. A competitive enzyme-linked immunosorbent assay showed that the SP ethanol extract binds to the programmed death-ligand 1 (PD-L1) in a concentration-dependent manner. SP extracts also promote the death of T-cell-mediated colorectal cancer cells[7]. Previous studies indicate that SP extract has an anti-cancer effect. As a result, we intend to investigate the preliminary effects of SP on quality of life in patients with solid cancer.

2. Methods

2.1. Trial design and recruitment

This is a protocol of a preliminary, open-label, single-arm, and single-dose clinical trial. The trial will be conducted at the Daejeon Korean Medicine Hospital of Daejeon University (Daejeon, Republic of Korea). Eligible participants will be recruited based on patients' interest at doctor's visits and through online clinical trial posters (hospital website, clinical trial center website) during the estimated recruitment period (May 2022 to April 2023). The clinical trial will last 12 weeks and will include 5 visits, including screening visit (Table 1 and Figure 1). Prior to study enrollment, investigators will explain the objective, study procedures, and potential benefits and risks to each eligible participant. Written informed consent will be obtained at the screening visit. The researchers will ensure that the trial is carried out in accordance with the principles of the Helsinki Declaration and Good Clinical Practice

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•Received : September 6, 2022 / Revised : October 25, 2022 / Accepted : November 2, 2022

Guidelines.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

(1) Patients aged 20–65 years old

(2) Those who have been diagnosed with solid cancer and have undergone, are currently undergoing, or have not received surgery, chemotherapy, or radiation therapy, and still have residual cancer

(3) Those who can take investigational products orally

(4) Those who show an activity status of 0–2 on the Eastern Cooperative Oncology Group Performance scale

(5) Those who voluntarily decide to participate and provide written informed consent after hearing and fully understanding the detailed explanation of the trial

(6) Those who can sufficiently communicate with the investigators about their symptoms or quality of life and fill out a questionnaire

(7) Those who follow up during the trial period

(8) Those with a life expectancyof ―3 months

2.2.2 Exclusion criteria

(1) Patients with symptomatic and uncontrolled epilepsy, central nervous system metastasis, or other malignancy now, or having a history of other malignancies (excluding cured basal or squamous cell skin cancer, cervical intraepithelial neoplasia, thyroid cancer, prostate cancer, and breast cancer) within 5 years of the screening visit

(2) Patients with uncontrolled hypertension (diastolic blood pressure 〉100 mmHg or systolic blood pressure 〉160 mmHg) or those with diabetes, active infection, and heart diseases such as symptomatic congestive heart failure and unstable angina

(3) Those with uncontrolled pleural effusion, ascites, or pericardial effusion

(4) Those who are taking or require psychotropic drugs to treat a major psychotic disorder (excluding insomnia disorder)

(5) People with alcoholism or drug dependence

(6) Those with a history of serious drug allergy or hypersensitivity to the investigational product (the main ingredient and its components)

(7) Women who are pregnant or lactating, who may be pregnant, who are planning to become pregnant, or of childbearing potential who do not agree to choose an appropriate method of contraception

(8) Those who have participated in other clinical trials within 6 months or plan to participate in other trials during the trial period

(9) Those with a medical condition that may affect the test results, or who is inappropriate for participation in this trial based on the judgment of the researcher

(10) Those who are or should be undergoing parenteral nutrition or tube feeding

2.2.3. Early termination and dropout criteria

Participants may withdraw from the clinical trial at any time by submitting a request for discontinuation. Participants will be removed if they are no longer able to participate due to adverse events, under the judgment of the investigator. Compliance rate under 70% will drop the participants. If participants take medicine or supplements that can affect the trial results, they will be removed.

2.3. Intervention

Participants who meet the eligibility criteria will visit the trial institution within 3 weeks after the screening. They will be given SP preparation, which is an ethanol 70% extract and green granule. Since our experimental study used 300 mg/kg/day of SP extract in mice[7], the daily dose of SP extract for humans was calculated as 1500 mg/day. It is based on the human body conversion of 300 ´ 60 (kg) ´ 0.08 = 1440 mg (/day). Accordingly, 2.0 g of the investigational product, including 1500 mg of SP extract and 500 mg of excipients, was determined as the daily dose. Participants will be instructed to take 2.0 g of SP granules (1 pack) once daily with sufficient water

within 30 minutes after breakfast. The participants will receive a 4-week prescription of the investigational product at each visits of 2, 3, and 4. The product is distributed 3 times over the course of 12 weeks along with a product intake schedule and ask participants to mark their daily intake. At each visit, the schedule sheet will be collected from the participants and a new sheet will be distributed. The product will be manufactured by Huons Foodience Co., Ltd. (Geumsan, Chungnam, Republic of Korea).

2.4. Outcome measures

The trial's primary outcome measure is quality of life of the participants. Except for the screening visit, this will be measured using the Korean version of the Functional Assessment Cancer Therapy-General questionnaire[8]. Secondary outcome measure include tumor markers for each cancer type, soluble PD-L1, the percentage of natural killer cells among lymphocytes, ratio of total T, T-helper and T-suppressor cells (CD4+/CD8+ among T cells), and B cells in lymphocytes, level of C-reactive protein, and tumor size via radiology examination. Radiological examination will be performed at visits 2 and 5, before and after administration of the investigational product. The other measures will be evaluated at all visits except for the baseline visit. For radiology examinations collected at visit 2, examination data up to 3 months in advance are also permitted. Safety will be monitored via hematological, liver and kidney function, and electrolyte tests, vital signs and physical examination at every visit except for the baseline visit. Furthermore, regardless of their relevance to the investigational product, all adverse events are collected at each visit, based on investigator examination and participant's self-report. Participants with adverse events are followed up until their condition stabilizes. The investigator will minimize adverse events through prompt and appropriate measures.

2.5. Sample size

This study is the first preliminary clinical trial to evaluate the effect of SP extract on quality of life in patients with solid cancer, there is no suitable literature for reference. The target sample size was determined to be 20 participants.

2.6. Statistical analysis

Full set analysis will be performed on all participants who were enrolled in the trial. Participants who took the product at least one time will be evaluated with the intent-to-treat principle. If necessary, data of participants who completed trials can be used as the ancillary results through per-protocol set analysis. The safety analysis includes all data obtained from participants who take the investigational product at least once. The last observation carried forward method will be used to handle the missing values. The significance level for the statistical significance test is set to 5%, and 2-sided tests will be performed. For pre-post comparison, depending on the normality of the data, a paired t-test or a Wilcoxon signed-rank test will be performed. Continuous variables are presented as mean (standard deviation) or median (interquartile range). Categorical variables are reported as frequencies (percentages). Interim analyzes will not be performed.

2.7. Data monitoring

A clinical research associate from the Korea Institute of Oriental Medicine (KIOM), which sponsored this study, will visit the institution on a regular basis to monitor protocol compliance, document reporting, recruitment rate, and adverse events during the trial period. The monitoring procedures and timetable will be in accordance with the KIOM monitoring standard operating procedure. Any issues will be discussed properly with the investigators. Data coding will be performed by one researcher and will be reviewed by the monitoring team.

2.8. Ethical consideration

This trial has been approved by the institutional review board (IRB) of Daejeon Korean Medicine Hospital of Daejeon University (approval number: DJDSKH-22-BM-06) and registered in Clinical

Research Information Service (registration number: KCT0007315). If the protocol requires modification, it will be approved by the IRB prior to any further implementation. Written informed consent will be obtained from all participants prior to proceeding with the study. Participants' personal information will be de-identified, and only those directly related to the research will have access to it. The results of this study will be published in peer-review journals or conference abstracts.

3. Discussion

This is a study protocol for a preliminary, open-label, single-arm, and single-dose clinical trial on patients with solid cancer being treated with an SP preparation. Recently, a 'paradigm shift' has taken place from the second-generation targeted cancer treatment to the immunotherapy. Moreover, the approval of the third-generation immunotherapy is increasing. The most popular targets for immunotherapy are immune checkpoint inhibitors, such as PD-1 and PD-L1 inhibitors. These have fewer side effects when compared to their therapeutic effect, have a longer half-life, and can be widely applied to various cancers and combination treatments[9, 10]. Accordingly, clinical trials assessing the efficacy of the combination therapy that focus on immune checkpoint inhibitors are being conducted worldwide. In addition, the concurrent administration of natural products and chemotherapy to patients with tumors has improved quality of life and reduced the side effects of anticancer drugs[6].

SP is a Korean traditional herbal substance that is widely used to treat the common cold, flu, and cough[1]. Traditional literature has reported that SP is anti-inflammatory, antioxidative, antibacterial, and antiviral[3, 4]. After the oral administration of SP to mice transplanted with colon cancer cells for 15 days, the KIOM research team has confirmed the inhibition of PD-1 and PD-L1 binding[7], which is the main mechanism of action of the immune checkpoint inhibitor[11]. This study aims to observe the effects of oral administration of SP preparations on patients with solid cancer via changes in quality of life and improvements in immune function. The results of this study are expected to provide preliminary evidence of the effect and safety of SP for patients with solid cancer.

Authors' contributions.

Conceptualization: HSC and JJ
Investigation: SP, EK, and JJ
Methodology: BL, ARK, JGC, HSC, and JJ
Project administration: JJ
Supervision: HSC
Writing-original draft: BL and SP
Writing-review & editing: ARK, EK, JGC, HY, HSC, and JJ
BL and SP have contributed equally.

Funding statement

This work is supported by the Korea Institute of Oriental Medicine (grant no. KSN2022230). The funding source will have no input regarding the interpretation or publication of the study's results.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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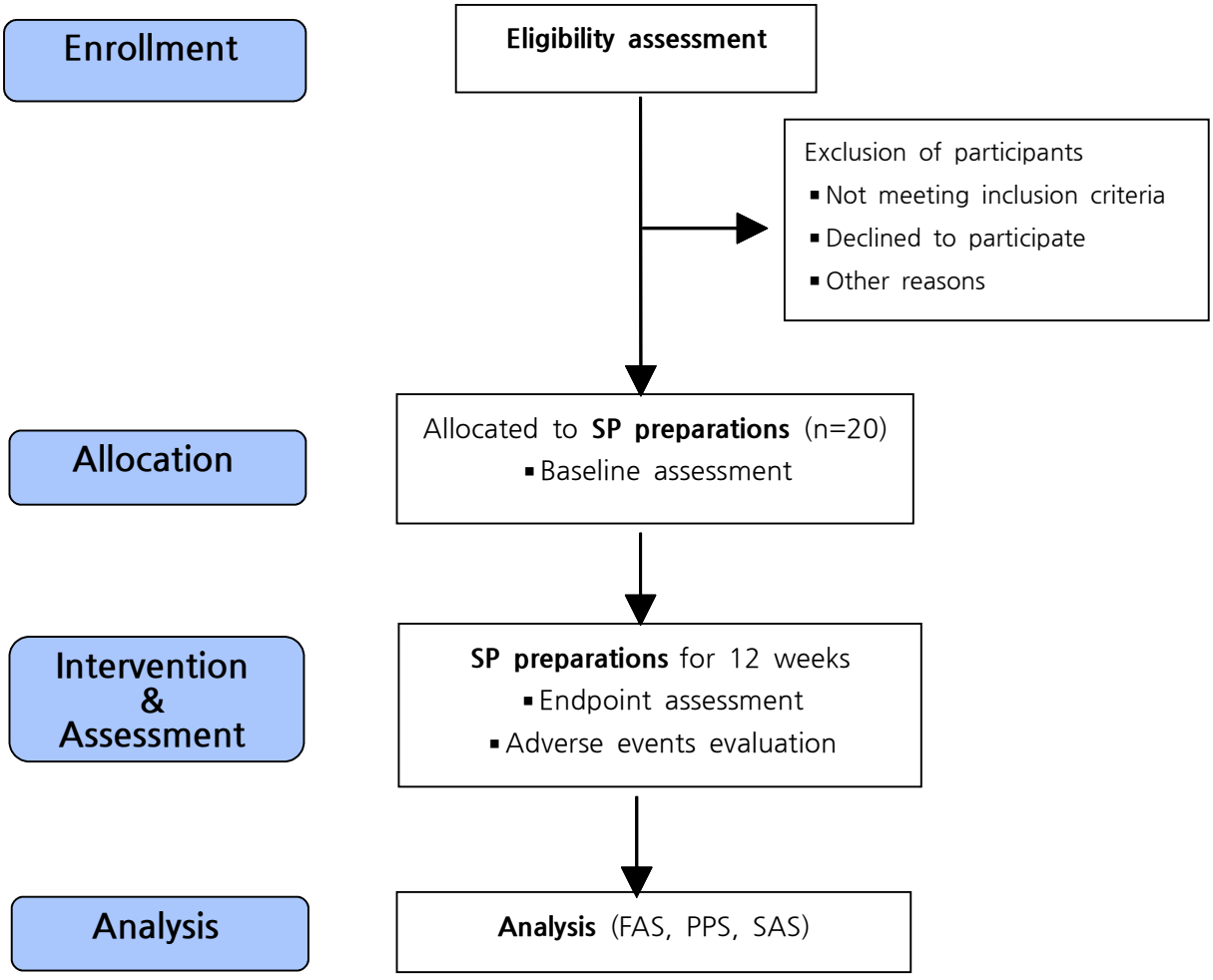
Fig. 1. CONSORT 2010 Flow Diagram



Abbreviations. FAS, full analysis set; PPS, per-protocol set; SAS, safety assessment set; SP, Salvia plebeia R. Br.

Table 1. Schedule of enrolment, interventions, and assessments

Contents	Visit 1 (screening) (−21 days ~)	Visit 2 (baseline) (Day 0)	Visit 3 (Week 4 ± 7 days)	Visit 4 (Week 8 ± 7 days)	Visit 5 (Week 12 ± 7 days)
Informed consent	√				
Eligibility screening	√				
Demographics and medical history taking	√				
Physical examination	√	√	√	√	√
Vital signs	√	√	√	√	√
Electrocardiogram	√				
ECOG performance status	√		√	√	√
SP prescription and distribution of dosing diaries		√	√	√	
Compliance check			√	√	√
FACT-G		√	√	√	√
Laboratory test*	√		√	√	√
Radiology examination		√			√
Adverse events monitoring		√	√	√	√

*including tumor markers, soluble PD-L1, natural killer cells, total T cells, T-helper cells, T-suppressor cells, and B cells in lymphocytes, C-reactive protein, hematological tests, liver and kidney function tests, and electrolyte tests; human chorionic gonadotropin urine test only for women in their childbearing years at the screening visit.
Abbreviations. ECOG, Eastern Cooperative Oncology Group; FACT-G, Functional Assessment Cancer Therapy-General; SP, Salvia plebeia R. Br.