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# Effectiveness and Safety of Pharmacopuncture therapy for chronic low back pain: A protocol for an assessor-blinded, pragmatic randomized controlled, pilot trial

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**Study protocol**

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## Abstract

# Background

Low back pain is a common musculoskeletal disorder worldwide with a lifetime prevalence of up to 80%, and Korean medicine treatment is often used for it. Chronic low back pain results in great personal, social, and economic burden. However, its cause is known to be non-specific. We will investigate the effectiveness and safety of pharmacopuncture for chronic low back pain since there is a current lack of research on this topic.

# Methods

This will be a pragmatic randomized, and assessor-blinded pilot clinical study. The participants will be randomly allocated to the treatment group (pharmacoupunture therapy with traditional Korean medicine) or to the control group (traditional Korean medicine). The duration of the clinical trial will be 9 weeks. The primary outcome will be measured using the visual analog scale; the secondary outcomes will include the Oswestry Disability Index, Patient Global Impression of Change, no worse than mild pain, and range of motion.

# Conclusions

We will evaluate the efficacy and safety of pharmacopuncture for chronic low back pain and will contribute to knowledge on the evidence-based treatment for it.

# Abberviations:

LBP: low back pain, IRB: Institutional Review Board, KMD: Korean medical doctor, TKM: Traditional Korean medicine, VAS: Visual Analog Scale, ODI: Oswestry Disability Index, PGIC: Patient Global Impression of Change, ROM: Range of motion, PRCT: pragmatic randomized controlled trial, SAE: serious adverse event

# Trial registration:

This study protocol was registered with the Korean National Clinical Research Information Service (CRIS) on July 17, 2023 (CRIS-KCT0008620). The participants will be retrospectively registered. https://cris.nih.go.kr/cris/search/detailSearch.do?seq=25180&search_page=L

## 1. Introduction

Low back pain (LBP) is a very common musculoskeletal disorder worldwide across all age groups, with a predominance in middle-aged people from the age of 40 to 69 years [1–3] and is more common in females. Chronic LBP is defined as back pain that lasts for more than 3 months [2, 4] and is used to describe a symptom related to pain between the 12th rib and the lower gluteal folds [4]. LBP can occur as a result of many causes, including trauma or repetitive motion damage, degenerative changes due to aging, or structural degeneration of the lumbar spine. However, since up to 85% of patients with chronic LBP are diagnosed with non-specific LBP, it is challenging to specify a definitive cause [4, 5]. Chronic LBP is a personal, social, and economic burden that accounts for a large portion of health care costs related to musculoskeletal pain [6]. It refers to not only the pain itself, but also a series of symptoms, such as depression, anxiety, and sleep disorders [1, 6].

LBP is the most common disease encountered at Korean medical institutions in South Korea [7, 8]. Although the use of pharmacopuncture in the treatment of LBP is thought to contribute greatly to public health, there is a current lack of research on the safety and effectiveness of pharmacopuncture for chronic LBP. We will attempt to conduct a practical randomized controlled study to determine the safety and effectiveness of pharmacopuncture used clinically for such frequently occurring chronic LBP.

## 2. Methods

2.1 Study design

This is a prospective, assessor-blinded, single-center, pragmatic randomized controlled trial (PRCT). The protocol ver 1.1 was approved by the Institutional Review Board (IRB) on June 19, 2023. Recruitment is scheduled to begin in July 2023, and the trial ends in December 2023. The participants will be recruited via placards on outdoor banners in Daejeon University Cheonan Korean Medicine Hospital and will receive written explanations and informed consent forms for the clinical trial protocol from a Korean medical doctor (KMD).

Blood tests for liver function, inflammation-related cells, and complete blood count and a test for human chorionic gonadotropin in urine will be performed.

A total of 44 participants who meet the eligibility criteria for this study will be randomly assigned in a 1:1 ratio to the treatment group (pharmacopuncture therapy with traditional Korean medicine [TKM]) or control group (TKM treatment). The intervention will begin within 1 week of the screening visit.

Based on the study group they will be randomized into, the participants will receive either interventional or control treatment for 8 weeks. The total duration of the clinical trial will be 9 week ± 5 days, and the efficacy and safety will be assessed at the 17th visit. A flowchart of the study is shown in Table 1 and Figure

1.

Table 1. Schedule for the enrollment, intervention, and assessments.

| | Study period | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Enrollment, Allocation | Intervention period | | | | | | | | | | | | | | | |
| | Week -1 | Week 0 (Baseline) | Visit | | | | | | | | | | | | | | | |
| | | | Week 1 ~ Week 8 | | | | | | | | | | | | | | | |
| | | | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | V16 |
| **Enrollment** | | | | | | | | | | | | | | | | | | |
| Checking the selection/exclusion criteria | ● | ● | | | | | | | | | | | | | | | | |
| Get consent form | ● | | | | | | | | | | | | | | | | | |
| Vital signs | ● | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Demographic surveys and body measurements | ● | | | | | | | | | | | | | | | | | |
| Medical history of lumbar and other body organs | ● | | | | | | | | | | | | | | | | | |
| Clinical laboratory test | ● | | ● | | | | | | | | | | | | | | | |
| L-spine X-ray | ● | | | | | | | | | | | | | | | | | |
| Randomized allocation | | ● | | | | | | | | | | | | | | | | |
| **Interventions** | | | | | | | | | | | | | | | | | | |
| Pharmacopuncture therapy with TKM | | | | | | | | | | | | | | | | | | |
| TKM | | | | | | | | | | | | | | | | | | |
| **Assessments** | | | | | | | | | | | | | | | | | | |
| Visual Analog Scale | ● | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Patient Global Impression of Change | | | | | | | ● | | | | ● | | | | ● | | | |
| no worse than mild pain | | | | | ● | | ● | | ● | | ● | | ● | | ● | | ● | |
| Range of motion | | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Oswestry Disability Index | | | ● | | | | ● | | | | ● | | | | ● | | | |
| Checking Adverse events | | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Confirmation of study stopping and dropout criteria | | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Visit schedule training | | | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | |

TKM= Traditional Korean medicine

2.2 Inclusion and exclusion criteria

The inclusion criteria will be as follows: age of 19 to 64 years; back pain ≥ 6 months; a visual analog scale (VAS) of back pain score ≥ 50 mm,; and agreement to participate in this trial and voluntary signing of a written informed consent.

The exclusion criteria will be as follows: a diagnosis of spinal metastases of tumors, acute fracture, and/or spinal dislocations; LBP caused by tumor, fibromyalgia, rheumatoid arthritis, and/or gout; a past history of other chronic diseases, such as stroke, myocardial infarction, kidney disease, and/or diabetic neuropathy; currently taking medication such as steroids, immunosuppressants, and/or psychiatric drugs; pain in other parts worse than LBP; pregnancy or breastfeeding; lumbar surgery within the last 3 months; participation in another clinical trials within 4 weeks; and spinal surgery scheduled during the test period.

2.3 Sample size calculation

This will be a pilot trial to explore the effect and safety of pharmacopuncture on chronic LBP. The evidence for the effect size in this study has been based on that by Park et al. (2021) [9]. The effect size for the evaluation variable (VAS, numerical rating scale for the neck) for chronic neck pain in that study has shown a distribution between 0.16 and 0.51. When the power is set to 80% and the effect size of the clinical study is conservatively considered to be 0.1 to 0.3, a total of 40 participants are planned to be recruited, with 20 people per group according to the suggestion of Whitehead et al. (2016) [10]. The dropout rate reported by Park et al. (2021) [9] was 3%, and considering the dropout rate of 5% in this clinical study, the final sample size to be recruited is set to 44 people, with 22 for each group.

2.4 Randomization and blinding procedures

Randomization will be performed using the block randomization method in the treatment and control groups at a ratio of 1:1. An independent statistician will randomly assign 22 individuals per group with the same probability of each object being selected using balanced block randomization without stratification. The generated randomization table will be held by a statistician independent of this trial, and the file will be protected from disclosure. The participants who meet all of the registration criteria will be randomly assigned a randomization identification code (e.g., LBP2023-R001, LBP2023-R002, and so on until LBP2023-R044) in the order generated by a computer-randomized program. The randomization number will be given to each participant and will indicate whether pharmacopuncture therapy with TKM or TKM alone shall be applied. The randomization code will be placed in an opaque envelope and stored in a locked cabinet. Once the researcher has sufficiently explained the clinical research to the participants and the latter have filled out the consent form to participate in the trial, after being screened for the inclusion and exclusion criteria, the researcher will open the random assignment envelope with the same number as the randomization number in front of the participants and assign the subject.

2.5 Interventions

The TKM treatment discussed in this study will include acupuncture, cupping, and infrared therapy. Acupuncture will be performed for 15 minutes. Simultaneously, infrared irradiation will be applied to the patient's acupuncture point. Cupping will be performed on the lumbar region for 5 minutes before or after acupuncture. The types of acupuncture and pharmacopuncture will be determined based on the clinical judgment of a KMD.

All eligible participants will receive treatment according to their allocated group (pharmacopuncture therapy with TKM or TKM alone) for 16 sessions during the treatment period. In principle, the procedure will be performed twice a week for 8 weeks. However, depending on the patient's condition, this may increase or decrease to once a week; treatment may be performed up to three times and at least once a week.

2.6 Outcome measures

The primary outcome will be the VAS score, which will be used to assess LBP at each visit. The secondary outcomes will be the average changes in the Oswestry Disability Index (ODI) score, Patient Global Impression of Change (PGIC) on treatment, range of motion (ROM), and no more than mild pain after treatment (V17) compared with the baseline (V1). The VAS scores and ROM will be measured at each visit. The ODI and PGIC will be measured at V1, V5, V9, V13, and V17, excluding V1 for the PGIC. No more than mild pain will be checked at V3, V5, V7, and so forth until V17. To ensure the participant’s safety, we will conduct laboratory tests at screening and at the end of the procedure (V17), such as that for liver function, complete blood count, and inflammation-related indicators, and evaluate vital signs at every visit. Safety assessments will be conducted at every visit.

2.6.1 VAS

VAS will be used to evaluate the intensity and frequency of pain on a line given to the participant. In general, a horizontal line on a non-marking line of 10 cm indicates “no pain” at the left end and “maximum pain imaginable” at the right end; the participant will mark a point on the line [8].

2.6.2 ODI

ODI will be used to evaluate functional disability due to LBP. It comprises 10 items, each of which comprising 6 questionnaires with a given score of 0 to 5 points. The higher the score, the more severe the disability [11].

2.6.3 PGIC

PGIC is a self-reported scale that compares a respondent’s improvement before and after treatment. It comprises seven questionnaires: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse [12].

2.6.4 ROM

ROM measures the angle of maximum active joint motion in which a participant can move without pain. Flexion, extension, bilateral rotation, and bilateral flexion angles will be measured while the participant is standing upright.

2.6.5 No more than mild pain

This is a method in which the participant subjectively responds to treatment and is an index expressing that there is a minimum clinically significant effect. It reflects improvement and satisfaction with treatment [13].

2.7 Data collection (Data analysis)

At screening, the participants will complete a questionnaire regarding their sociodemographic characteristics, provide their lumbar spine medical history within the past 6 months and their drug history within the past 4 weeks. The participants will undergo L-spine X-ray, and the aforementioned laboratory tests. The personal information and data will be managed by the investigators. The monitoring of data and research performances will be conducted regularly by researchers from the Cheonan Korean Medicine Hospital of Daejeon University (Cheonan, Republic of Korea). The final trial dataset will be accessible to statisticians and the principal investigator. All information regarding the participants and interventions will be kept confidential. All documents related to the clinical trial will be recorded and classified using an identification code instead of the participant's name.

2.8 Statistical analysis

Statistical analysis will be primarily based on the principle of a full analysis set. Missing values will be analyzed via the last observation carried forward method. The baseline values before treatment and the changes in VAS score after 9 weeks of treatment will be measured for both groups. Descriptive statistics will be presented as mean, standard deviation, median, and minimum and maximum values. Continuous data will be tested using t-tests or Wilcoxon's rank sum tests. Categorical data will be analyzed using the chi-square test or Fisher's exact test. The significance level will be set at a P-value of <.05 and the confidence interval at 95%. The statistical analyses will be performed using the SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY, USA).

Subgroup analysis of demographic variables (e.g., sex, age, duration of illness, and so on) can be performed as needed. On every visit, the researchers conduct a safety assessment by analyzing the symptoms and duration of adverse and serious adverse events (SAEs) that are thought to be associated with treatment. All of the adverse events and SAEs will be recorded with a detailed description of patient symptom reporting and researcher observation.

2.9 Withdrawal and dropout

If the participant does not meet the inclusion or exclusion criteria or withdraws their consent or if the participant's continued participation is judged as inappropriate, he/she will be excluded from the study. In addition, all of the participants who become pregnant during the study period will immediately discontinue the clinical trial. The researchers will record the reason for any interruption in the intervention and whether each participant completed the study.

2.10 Concomitant treatment

If LBP is severe during the clinical research period, non-invasive treatments such as physical therapy, manual therapy, and drugs are allowed under the judgment of the researcher, but invasive treatments such as surgery and injection are prohibited. The details of the concomitant treatment will be recorded in the CRF for analysis. However, traditional Korean medicine treatment for LBP is prohibited outside of this study.

2.11 Safety

The occurrence of all adverse events will be assessed at each visit. The participants will be monitored for undesirable, unintended symptoms, signs, illnesses, and pre- and post-treatment clinical examinations. The number and percentage of participants who experience at least one adverse event will be calculated.

2.12 Ethics

This study is designed based on the Helsinki Declaration and the Korean Clinical Practice Guidelines, and it was approved by the Korean IRB of DUCKMH (approval number: DJUMC-2023-BM-06-1). This study protocol is registered with the Korean National Clinical Research Information Service (CRIS) (CRIS-KCT0008620). The participants will receive a fully written explanation of the study protocol and an informed consent form. The participants may be required to quit the study and advised to receive appropriate treatment in case of SAEs or adverse reaction, upon which they will be reported to the IRB of the hospital. They will be allowed to withdraw their consent at any time for any reason or discontinue their participation on a voluntary basis.

## 3. Discussion

The prevalence of LBP is over 80% in a person's lifetime [4,5]. Its high prevalence, high recurrence rate, and great functional disability facilitate chronic pain [1,4]. It is believed that the more common causes in females are pain related to osteoporosis, menstruation, and pregnancy [2].

Schwartz and Lellouch first used the term in 1967 while comparing explanatory and pragmatic trials. An explanatory trial aims to verify and understand the causal relationship of clinical hypothesis, and a pragmatic trial aims to determine the choice of treatment method [14, 15]. In PRCTs, the study design simulates the actual clinical situation as much as possible and often does not use patients or doctor blinding. In many cases, both the treatment and control groups undergo usual care; the treatment for which the effect is to be evaluated is applied to the treatment group. Since PRCT research evaluates multidimensional results by complex treatment, it is suitable for clinical research in TKM [16]. This is a pragmatic clinical study wherein the effects of pharmacopuncture therapy for chronic back pain will be evaluated. The depth, type, concentration, and amount of pharmacopuncture should be selected according to the clinical judgment of the Korean medicine doctor. All acupoints and pharmacopuncture points at the time of the procedure, the type of pharmacopuncture used, and the total dose (mL) will be recorded.

Pharmacopuncture is a treatment method that combines acupuncture and herbal medicine and maximizes the effect of treatment through purified herbal extracts injection into acupoints [17]. The physical effect of stimulating acupoints and the chemical effect of herbal extracts are expected to create a synergistic effect [18]. Although various methods are recommended for the treatment of chronic LBP, there is currently no clear cause and treatment of choice [4]. However, while pharmacopuncture is highly useful in clinical practice, a few studies have been conducted on it, with a consequent lack of research on its effect on chronic LBP [19]. Thus, this study may provide insights into this treatment evidence for future large-scale clinical trials that will investigate the therapeutic effects of the pharmacopuncture on chronic LBP.

## Abbreviations

LBP: low back pain, IRB: Institutional Review Board, KMD: Korean medical doctor, TKM: Traditional Korean medicine, VAS: Visual Analog Scale, ODI: Oswestry Disability Index, PGIC: Patient Global Impression of Change, ROM: Range of motion, PRCT: pragmatic randomized controlled trial, SAE: serious adverse event

## Declarations

### Ethics approval and consent to participate

This study protocol is designed according to the Helsinki Declaration and the Korean Clinical Practice Guidelines. This clinical trial protocol was reviewed and approved by the institutional review board of the Daejeon University Cheonan Korean Medicine Hospital (DJUMC-2023-BM-06-1) as protocol ver1.1 on June 19, 2023. This study protocol was prepared according to the Standard Protocol Items: Recommendations for Intervention Trials. All participants will provide voluntary written informed consent after fully discussing potential benefits and risks before participating.

### Consent for publication

Not applicable

### Availability of data and materials

Not applicable

### Competing Interests

The authors declare no competing interest.


### Funding

This study was supported by the Daejeon University Research Grants (2023).


### Trial status

This clinical trial will be performed during the recruitment stage, which begins in July 2023 and is expected to be completed in December 2023. This trial was registered at the Clinical Research Information Service (CRIS) of the Republic of Korea on July 17, 2023 (CRIS-KCT0008620).

### Authors' contributions

HL and JHK designed, administered, and supervised the study protocol. RHY supervised and critically revised the manuscript. YYC, YKK, and ESW developed the protocol, and YYC drafted the manuscript. All of the authors read and approved the final version of the manuscript.


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## Figures

| | STUDY PERIOD | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | | | | | Close-out |
| **TIMEPOINT** | $-t_1$ | 0 | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | .. . | $t_{16}$ | $t_{17}$ |
| **ENROLMENT:** | | | | | | | | | | |
| **Eligibility screen** | X | | | | | | | | | |
| **Informed consent** | X | | | | | | | | | |
| ***X-ray of Lumbar spine*** | X | | | | | | | | | |
| ***Allocation*** | | X | | | | | | | | |
| **INTERVENTIONS:** | | | | | | | | | | |
| ***Pharmacopuncture with TKM*** | | | ♦— | — | — | — | — | — | —♦ | |
| ***TKM*** | | | ♦— | — | — | — | — | — | —♦ | |
| **ASSESSMENTS:** | | | | | | | | | | |
| ***Visual Analog Scale*** | | | X | X | X | X | X | | X | X |
| ***Patient Global Impression of Change*** | | | | | | | X | | | X |
| ***Oswestry Disability Index*** | | | X | | | | X | | | X |
| ***No worse than mild pain*** | | | | | X | | X | | | X |
| ***Range of motion*** | | | X | X | X | X | X | | X | X |

**Figure 1**

SPRIT Figure show schedule of enrolment, interventions, and assessments

The “X” refers to what is done in the given period.
During the omitted period, the same evaluation items are repeated in $t_2$~$t_5$, $t_6$~$t_9$, $t_{10}$~$t_{13}$, and $t_{14}$~$t_{17}$.
Abbreviations: TKM, Traditional Korean medicine; SPIRIT, Standard protocol Items: Recommendations for Intervention Trials