Journal of Pain Research

Dovepress
Taylor & Francis Group

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STUDY PROTOCOL

# Efficacy, Safety, and Economic Evaluation of Gamidaeganghwal-Tang in Patients with Knee Osteoarthritis: Protocol for a Multicenter, Randomized, Double-Blind, Controlled Trial

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**Purpose:** Knee osteoarthritis (KOA) is a common degenerative joint disease that severely affects quality of life. Gamidaeganghwal-tang (GMDGHT), a traditional Korean herbal medicine, has been widely used to treat joint pain and stiffness. However, robust clinical evidence for its efficacy and safety is lacking. This trial protocol aims to evaluate the efficacy, safety, and cost-effectiveness of GMDGHT compared to a placebo in patients with degenerative KOA.

**Trial Design and Methods:** This protocol describes a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial. A total of 160 participants (80 per group) will be recruited from four Korean medicine hospitals. Eligible participants aged 40–70 years must have radiographic KOA (Kellgren-Lawrence grades I–III) and a Korean Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC) score ≥30. Participants will be randomly assigned 1:1 to receive either GMDGHT or placebo granules (10 g, orally, three times daily) for 12 weeks, followed by a 12-week observation period. Assessments will be conducted at baseline and at weeks 4, 8, 12, and 24. The primary outcome will be the change in total K-WOMAC score from baseline to week 12. Secondary outcomes include pain intensity (100-mm visual analog scale), quality of life using the EuroQol 5-dimension 5-level (EQ-5D-5L), patient satisfaction, rescue medication use, and cost-effectiveness from societal and healthcare perspectives. Safety will be monitored through adverse events and laboratory findings.

**Discussion:** This trial will rigorously evaluate the efficacy, safety, and cost-effectiveness of GMDGHT for KOA. Despite efforts to maintain blinding with identically packaged placebo granules, subtle differences in taste or texture may challenge complete participant blinding. Restrictions on concomitant therapies may also influence adherence. Nonetheless, this study is designed to minimize potential bias and generate reliable clinical evidence on GMDGHT's role as a complementary or alternative therapeutic option for KOA.

**Trial Registration Number:** KCT0008486 (Clinical Research Information Service of the Republic of Korea), registered on 01 June 2023.

**Ind Approval Number:** 101414 (Approved by the Ministry of Food and Drug Safety, Republic of Korea) on April 19, 2023.

**Keywords:** degenerative joint disease, Gamidaeganghwal-tang, knee osteoarthritis, randomized controlled trial, herbal medicine, placebo-controlled trial

https://doi.org/10.2147/JPR.S594693
Received: 30 January 2026
Accepted: 4 April 2026
Published: 16 April 2026

# Introduction

Knee osteoarthritis (KOA) is one of the most common degenerative musculoskeletal disorders worldwide, particularly prevalent in aging populations. It is increasingly recognized as a whole-joint disease involving not only cartilage degeneration, synovial inflammation, osteophyte formation, and joint space narrowing, but also meniscal pathology, subchondral bone remodeling, and biomechanical alterations in periarticular tissues. Major risk factors for KOA include aging, female sex, obesity, metabolic syndrome, genetic predisposition, joint malalignment, repetitive joint stress, and previous joint injuries. Epidemiological studies estimate the prevalence of radiographic KOA in middle-aged and older adults at approximately 35.1% and 37.4% in Korea and the United States.[1,2] KOA-related healthcare expenditures have increased by an average of 5.7% annually since 1996, reaching approximately USD 8 billion in 2016.[3] These clinical and economic burdens highlight the importance of developing effective, safe, and accessible therapeutic strategies.

In traditional East Asian medicine, the pathophysiology of knee disorders is closely linked to the meridian system of the liver, kidneys, and tendons. Classical texts such as the *Huangjenaegyeongsomun* describe the knee as "the mansion of the tendons", and note that impairment in liver and kidney function, particularly owing to aging, can weaken sinews and bones, predisposing individuals to degenerative joint diseases. Traditional nosology lists various knee-related conditions, reflecting both the localized and systemic origins of pain and swelling.[4] Consequently, treatment principles emphasize replenishing qi and blood, warming meridians, dispelling wind-dampness, and tonifying the liver and kidneys under chronic degenerative conditions.

*Gamidaeganghwal-tang* (GMDGHT) is a modified herbal formulation based on the classical prescription *Daeganghwal-tang*. Traditionally, *Daeganghwal-tang* has been prescribed for wind-damp bi-syndromes marked by joint pain, swelling, and stiffness. Historical materia medica, such as the *Bangyak Hapbyeon* record its utility in rheumatoid-type arthralgia, polyarthritis, neuralgia, and degenerative KOA.[5] The addition of specific herbs to GMDGHT enhances anti-inflammatory and analgesic properties, making it a plausible candidate for the management of KOA.

Preclinical studies have provided mechanistic support for this clinical rationale. In collagen type II–induced arthritis models, the combined use of *Ganghwal* (*Ostericum koreanum* Maximowicz) and *Dokhwal* (*Aralia continentalis* Kitagawa)—key components of GMDGHT—significantly suppressed IgG/IgM production and reduced anti-collagen antibody titers, demonstrating immunomodulatory effects.[5] Additional studies using the parent formula *Duhuo Jisheng-tang* showed inhibition of the NLRP3/NF-κB pathway[6] and Notch1-mediated NLRP3 activation,[7] mechanisms directly relevant to cartilage degeneration and synovial inflammation in KOA.

Although large-scale randomized trials are still lacking, GMDGHT has been used in routine clinical practice at a single Korean Medicine hospital over the past three years. However, no prospective randomized studies have formally evaluated its efficacy and safety.

To address this gap in evidence, we designed a randomized double-blind placebo-controlled trial to evaluate the efficacy and safety of GMDGHT granules in patients with radiographically confirmed KOA. The trial will evaluate changes in knee pain and function using validated outcome measures, while monitoring safety. In addition, this study includes an economic evaluation component. The dosage was determined based on routine clinical practice at Kyung Hee University Korean Medicine Hospital, with the aim of enhancing practical applicability.

# Trial Design and Methods

## Methods and Design

This study is a multicenter, randomized, double-blind, parallel-group clinical trial designed to assess the efficacy, safety, and cost-effectiveness of GMDGHT compared with placebo in patients with degenerative KOA. A total of 160 participants (80 in each group) will be recruited from four institutions: Kyung Hee University Hospital in Gangdong, Kyung Hee University Medical Center, Pusan National University Korean Medicine Hospital, and Daegu Haany University Korean Medicine Hospital. The overall trial duration is 24 weeks for each participant comprising 12 weeks of treatment and 12 weeks of follow-up (Table 1). This protocol complies with the Declaration of Helsinki and Korean Good Clinical Practice guidelines. Written informed consent will be obtained from all participants prior to any study-

**Table 1** Schedule of Enrolment, interventions, and Assessments

| | **Screening** | **STUDY PERIOD** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Enrollment** | **Allocation** | **Post-Allocation** | | | **Follow-Up** | | |
| Time point (Weeks) | **−2 ~** | **0†** | **4†** | **8†** | **12†** | **16†** | **20†** | **24†** |
| Visit | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** |
| ENROLMENT: | | | | | | | | |
| Informed consent | X | | | | | | | |
| Demographic Data Collection | X | | | | | | | |
| *Medical History and Prior Medication Review | X | | | | | | | |
| Physical Examination | X | | | | | | | |
| Confirmation of ACR Criteria | X | | | | | | | |
| **X-ray Examination | X | | | | | | | |
| Eligibility Assessment | X | | | | | | | |
| Allocation | | X | | | | | | |
| INTERVENTIONS: | | | | | | | | |
| Gamidaeganghwal-tang | | | | | | | | |
| Placebo | | | | | | | | |
| Efficacy Assessment: | | | | | | | | |
| *100-mm Pain VAS* | | X | X | X | X | | | X |
| *K-WOMAC* | X | X | X | X | X | | | X |
| *EQ-5D-5L* | | X | X | X | X | X | X | X |
| *Economic Evaluation* | | X | X | X | X | | | X |
| *Satisfaction assessment* | | | | | X | | | X |
| Safety Assessment: | | | | | | | | |
| *Anthropometric Measurements* | X | | | | X | | | X |
| *Vital sign* | X | X | X | X | X | | | X |
| ****Laboratory test and electrocardiography* | X | | | | X | | | |
| *Concomitant medications* | | X | X | X | X | X | X | X |
| *Adverse Events Assessment* | | X | X | X | X | X | X | X |
| *****Pregnancy test* | X | | | | | | | |
| *Randomization* | | X | | | | | | |
| *Cold-Heat Pattern identification* | X | | | | | | | |
| *Investigational Product Dispensation* | | X | X | X | | | | |
| *Rescue Medication Dispensation* | | X | X | X | | | | |
| *Provision of Drug Administration Diary* | | X | X | X | | | | |

(*Continued*)


https://doi.org/10.2147/JPR.S594693

**Table 1** (Continued).

| | Screening | STUDY PERIOD | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Enrollment | Allocation | Post-Allocation | | | Follow-Up | | |
| *****Medication Adherence* | | | X | X | X | | | |
| *Blinding Maintenance Check* | | | | | | | | X |

**Notes**: X indicates that the corresponding assessment or procedure is scheduled at the specified visit., †Allows (±7 days) on specified days, VAS=Visual Analog Scale, K-WOMAC=Korean Western Ontario and McMaster, VAS=Visual Analog Scale, EQ-5D5L:European Quality of Life 5-dimension 5-level scale, *Surgical/allergy history (2 years), prior meds (3 months), wash-out (2–4 weeks if prohibited drugs used), **Bilateral knee AP and Lat X-rays; prior images within 4 weeks of screening may be used., ***Complete blood cell count, Blood chemistry examination and urinalysis, ****Urine HCG test performed only on women of childbearing age, *****Compare, check and record the remaining amount of investigational drug.

related procedures. The protocol has been approved by the Institutional Review Board (IRB) of each participating site (IRB approvals: Kyung Hee University Hospital at Gangdong [KHNMCOH202208001002-HE001]; Kyung Hee University Medical Center [KOMCIRB202305002001-HE003]; Pusan National University Korean Medicine Hospital [PNUKHIRB202306002001-HE002]; Daegu Haany University Korean Medicine Hospital [DHUMC-D-23006-PRO-01]).

In the event of trial-related harm, appropriate medical care will be provided, and compensation will be handled in accordance with Korean clinical trial regulations and institutional guidelines.

This study protocol was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[8]

## Investigational Product

GMDGHT is manufactured as granule packets (10 g each) in a Good Manufacturing Practice (GMP)-compliant facility. The formulation contains blended and processed dried herbal ingredients (Table 2). Placebo packets contain inert

**Table 2** Components of GMDGHT Granules

| Scientific Name (Latin Name) | Amount (g) |
|---|---|
| *Lonicera japonica* Thunberg (Lonicerae Flos) | 4.46 |
| *Taraxacum officinale* Weber (Taraxaci Herba) | 4.46 |
| *Ostericum koreanum* Maximowicz (Osterici seu Notopterygii Radix et Rhizoma) | 2.68 |
| *Cimicifuga heracleifolia* Komarov (Cimicifugae Rhizoma) | 2.68 |
| *Aralia continentalis* Kitagawa (Araliae Continentalis Radix) | 1.79 |
| *Atractylodes macrocephala* Koidzumi (Atractylodis Rhizoma Alba) | 1.25 |
| *Sinomenium acutum* Rehder et Wilson (Sinomeni Caulis et Rhizoma) | 1.25 |
| *Atractylodes lancea* De Candlle (Atractylodis Rhizoma) | 1.25 |
| *Angelica gigas* Nakai (Angelicae Gigantis Radix) | 1.25 |
| *Glycyrrhiza uralensis* Fischer (Glycyrrhizae Radix et Rhizoma) | 1.25 |
| *Poria cocos* Wolf (Poria Sclerotium) | 1.25 |
| *Alisma orientale* Juzepzuk (Alismatis Rhizoma) | 1.25 |
| *Clematis chinensis* Osbeck (Clematidis Radix) | 1.25 |
| **Dry weight of GMDGHT water extract** | 5.0 |
| Lactose Monohydrate | 2.7 |
| Corn Starch | 1.3 |
| **Excipients (inactive constituent)** | 5.0 |
| **Total** | 10.0 |

**Abbreviation**: GMDGHT, Gamidegangwhal-tang.

**Table 3** Ingredients of Placebo Granules

| Ingredients | Amount (g) |
|---|---|
| *Lactose monohydrate* | 5.00 |
| *Corn starch* | 4.48 |
| *Cocoa color* | 0.15 |
| *Caramel color* | 0.15 |
| *Gardenia yellow color* | 0.12 |
| *Ginseng flavor powder* | 0.10 |
| **Total** | 10.0 |

**Note**: The placebo granules contained no active herbal ingredients and were manufactured to be indistinguishable from the investigational product in appearance, color, and taste.

excipients such as lactose monohydrate, corn starch, and colorants to mimic the appearance, texture, and taste of GMDGHT (Table 3). The ginseng flavor powder included in the placebo formulation was used solely to mimic sensory characteristics and does not contain pharmacologically active components. Both products were packaged in identical materials and labeled according to the clinical trial regulations. Participants randomized to the GMDGHT group will receive one packet (10 g) thrice daily for 12 weeks, whereas those in the placebo group will receive an identical packet at the same frequency and duration.

## Participants

### Inclusion Criteria

Individuals will be eligible to participate in this study if they meet all the following criteria:

(i) Adults aged between 40 and 70 years;
(ii) experiencing knee pain due to degenerative KOA for more than three months;
(iii) Diagnosed with KOA according to the American College of Rheumatology classification criteria for osteoarthritis of the knee[9] and confirmed as Kellgren-Lawrence grade I to III on plain X-ray of the target lesion;[10]
(iv) Total Korean Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC) score of ≥30 at screening;[11,12]
(v) Willingness to discontinue existing KOA treatment and cooperate with study requirements;
(vi) Individuals who have received a detailed explanation of the study, voluntarily agree to participate, and provide written informed consent;
(vii) Individuals with unilateral KOA or bilateral KOA who can designate a target lesion based on the following criteria:
- If both knees meet the inclusion and exclusion criteria, the target lesion will be designated according to the following hierarchy:
  (a) The knee with the higher Kellgren-Lawrence grade will be selected as the target lesion.
  (b) If both knees have the same Kellgren-Lawrence grade, the knee with the greatest self-reported subjective pain during the screening will be designated as the target lesion.
  (c) If both criteria ((a) and (b)) are identical, the right knee will be designated as the target lesion.

### Exclusion Criteria

Participants will be excluded from the study if they meet any of the following criteria:

(i) History of knee joint trauma within six months prior to screening,
(ii) History of knee joint surgery or planned knee surgery during the clinical trial period, and (iii) history of intra-articular injections, including:

- Corticosteroids injection within six months prior to screening;
- Hyaluronic acid injection within six months prior to screening;

(iv) Suspected presence of the following diseases based on physical examination and diagnostic tests:

- Rheumatoid arthritis, autoimmune disease, septic arthritis, inflammatory joint disease, gout, recurrent pseudogout, Paget's disease, joint fracture, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary osteochondrosis, genetic disorders (eg, hyperkinesia), or collagen gene abnormalities

(v) Presence of musculoskeletal disorders that may affect the study outcomes, such as hip or spine-related conditions, as determined by the investigator;
(vi) Individuals undergoing treatment for mental disorders such as depression or schizophrenia;
(vii) Presence of liver disease, defined as aspartate transaminase (AST) or alanine transaminase (ALT) levels exceeding twice the upper limit of the institution's normal range;
(viii) Presence of renal disease, defined as serum creatinine levels >2.0 mg/dL;
(ix) Presence of severe gastrointestinal disorders, cardiovascular disease, uncontrolled hypertension or diabetes mellitus, severe renal or liver disease, or hemorrhagic disorders that could interfere with treatment;
(x) Known hypersensitivity or allergic reactions to the investigational drug components;
(xi) Presence of lactose intolerance, galactose malabsorption syndrome, or lactase deficiency;
(xii) History of hypersensitivity to piroxicam, aspirin-induced asthma, or a history of allergic reactions such as urticaria, rhinitis, or angioedema triggered by aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs);
(xiii) Current use of herbal medicines, dietary supplements, or herbal formulas containing active ingredients that overlap with the investigational product;
(xiv) Pregnancy or lactation;
(xv) Idividuals deemed unsuitable for herbal medicine therapy at the discretion of the investigator;
(xvi) Participation in another clinical trial within four weeks prior to this study or within five times the half-life of another investigational drug, whichever is longer;
(xvii) Individuals who have difficulty discontinuing NSAIDs or other analgesic medications;
(xviii) Any other conditions that the investigator considers inappropriate for trial participation

## Procedure

A total of 160 participants will be recruited through various media sources including hospital websites, local newspapers, online advertisements, and outpatient clinics. Screening assessments will include a thorough history taking, physical examinations, knee radiography, and completion of the K-WOMAC questionnaire. Eligible and consenting participants will be randomly allocated (1:1) to either the GMDGHT or the placebo group. Baseline data collection (Visit 1) will occur at week 0, followed by subsequent visits at weeks 4 (Visit 2), 8 (Visit 3), and 12 (Visit 4) to reassess the efficacy and safety outcomes. After the 12-week treatment period, the participants will enter a follow-up phase until week 24, with interim phone checks at weeks 16 and 20 (Visit 5 and 6), and a final in-person evaluation at week 24 (Visit 7). Throughout the study, adverse events, treatment adherence, and concomitant medications will be monitored and documented using case report forms (Table 1). Treatment adherence will be assessed by comparing the amount of investigational product dispensed with the amount returned at each visit, and adherence will be reported as a percentage.

## Interventions

Participants assigned to the GMDGHT group will ingest one packet (10 g) orally three times daily (morning, noon, and evening), approximately 30 min after meals for 12 weeks. Those in the placebo group will follow the same schedule with identically packaged inert packets. Both groups will be instructed to maintain regular dietary and activity patterns to minimize confounding effects.

## Concomitant Treatment and Participant Drop-Out

To ensure accurate outcome assessments, participants will not use additional analgesics, NSAIDs (including topical agents and patches), antidepressants, anticonvulsants, or intra-articular steroid injections during the 12-week treatment period, unless deemed necessary by the investigator. Acupuncture, moxibustion, cupping, and physical therapy are prohibited for treating knee pain. However, medications for stable conditions unrelated to KOA (eg, antihypertensives) may be continued at a stable dose.

All medications taken during the trial must be recorded in a case report form (CRF), and their dosages should remain unchanged whenever possible. If a participant requires prohibited treatment, they must be withdrawn from the study immediately for reasons documented in the CRF.

Participants will also be withdrawn if they experience serious adverse events, meet the newly identified exclusion criteria, request discontinuation, or deviate significantly from the protocol. Those who discontinue early will undergo a termination visit for the final safety and efficacy assessments.

## Primary Outcome Measurement

The primary outcome will be the change in total K-WOMAC score from baseline to week 12. The K-WOMAC is composed of 24 items across three subdomains—pain, stiffness, and physical function—each rated on a 5-point Likert scale. Higher scores indicate more severe symptoms. The between-group difference in the mean change in total K-WOMAC score will serve as the principal indicator of the effectiveness of GMDGHT relative to placebo.

## Secondary Outcome Measurements

Secondary endpoints will include the total K-WOMAC score at weeks 4, 8, and 24, changes in knee pain measured on a 100-mm visual analog scale, participants' general health status measured by the EuroQol 5-dimension 5-level (EQ-5D-5L) survey; and treatment satisfaction questionnaires completed at the end of the 12-week treatment and at week 24. Additional secondary analyses will include the amount of rescue medication used and the economic evaluation of direct and indirect costs. The use of rescue medication will also be considered as a potential covariate in the analysis to adjust for its impact on outcome measures.

## Randomization and Allocation Concealment

Block randomization (using a block size of four) will be performed by an independent statistician not otherwise involved in the study. The randomization list will be sealed in opaque, sequentially numbered envelopes. Once a participant is confirmed to be eligible at the end of the screening phase, the next envelope will be opened by a designated study coordinator, and the participant will be assigned to the appropriate group according to the code. The study team members responsible for the outcome assessments will be blinded to each participant's assignment.

## Blinding

Because both GMDGHT and placebo will be packaged in visually identical packets, participants, investigators, and outcome assessors will remain blinded to group assignments, thereby preserving the double-blind design. In rare and urgent situations in which medical management necessitates unblinding, the allocation code may be broken only for that specific participant, and the circumstances will be documented in the case report form. In addition, to assess the success of blinding, participants will be asked at the final visit to guess their assigned group. The success of blinding will be

evaluated by comparing the distribution of guesses between groups to assess whether allocation concealment was maintained.

## Economic Evaluation

To assess the cost-effectiveness of the treatment, a trial-based economic evaluation will be conducted from healthcare system and societal perspectives over the 24-week study period. A cost-utility analysis will be performed to evaluate both the quantity and quality of life using quality-adjusted life years (QALYs). The main analysis will be the incremental cost-utility ratio (ICUR), calculated based on the difference in total costs and QALYs between the GMDGHT and placebo groups. The costs incurred during the study period will be collected and categorized into direct medical costs, direct non-medical costs, and indirect costs (ie, productivity losses). Direct medical costs will be estimated based on treatment-related healthcare expenditure. Direct nonmedical costs will be assessed via patient surveys. Indirect costs will be measured using the validated Korean version of the Institute for Medical Technology Assessment Productivity Cost Questionnaire (iPCQ) to estimate productivity losses.[13]

## Safety Assessment

Safety will be assessed through the collection and analysis of adverse events (AEs), laboratory test results, vital signs, electrocardiogram (ECG) findings, and, when applicable, EQ-5D-5L questionnaires. All new symptoms, signs, or abnormal laboratory findings that occur during the trial period will be documented regardless of their causal relationship to the investigational product.

All AEs will be coded and categorized according to their intensity and assessed for causality, which will be classified into six categories: definitely related, probably related, possibly related, unlikely related, not related, and unknown due to insufficient information. Safety will be assessed through AEs, laboratory tests, vital signs, and electrocardiogram (ECG) findings. All new symptoms, signs, or abnormal laboratory findings occurring during the trial period will be documented regardless of their causal relationship to the investigational product. AEs will be coded and categorized according to intensity and causality. Laboratory tests, vital signs, and ECG findings will be assessed at the predefined study visits shown in Table 1.

When adverse events are reported, participants will be asked to retrospectively complete the EQ-5D-5L questionnaire to assess their perceived health status at the time of the event. This will be done only for AEs considered possibly, probably, or definitely related to the investigational product.

## Data Collection and Management

All participant data, including demographics, physical and laboratory findings, and questionnaires, will be recorded in case report forms (CRFs). Two trained staff members will verify the accuracy and completeness of the CRFs. Data will be stored in secure databases, with access limited to authorized personnel. Any protocol deviations, adverse events, or discrepancies in documentation will be noted and resolved according to Good Clinical Practice guidelines. Regular monitoring visits will be conducted to ensure data integrity and compliance with the study protocol.

## Sample Size Calculation

This study is designed as a superiority trial to demonstrate that GMDGHT is clinically more effective than a placebo in patients with degenerative KOA. The required sample size was calculated under the assumption of a two-sided significance level ($\alpha$) of 5% and a type II error ($\beta$) of 20%, corresponding to 80% statistical power. The primary hypothesis tested was that there would be a statistically significant difference in treatment effects between the two groups, with the null hypothesis stating that the mean difference between the groups is zero ($H_0$: $\mu c - \mu t = 0$), and the alternative hypothesis indicating inequality ($H_1$: $\mu c - \mu t \neq 0$).

A previous randomized controlled trial[14] reported a standard deviation of 21.2 for the K-WOMAC score at 12 weeks in patients with KOA. Based on prior studies suggesting that the minimal clinically important difference (MCID) for WOMAC scores ranges from 9.1 to 12, the expected effect size in this study was set at 10.55, which is the average of

these reported values. Although MCID values may vary depending on population characteristics, the selected value falls within the reported range and was considered clinically meaningful for this study.

Based on this assumed difference and the standard deviation, the calculated sample size per group was 79.729 participants. Considering a dropout rate of 20%, the final sample size was 80 participants in each group. Thus, 160 participants (80 each in the GMDGHT group and 80 in the placebo group) will be enrolled in this study.

## Statistical Analysis

This study is designed as a superiority trial to evaluate whether Gami-Daeganghwal-tang granules provide superior clinical benefits compared with placebo in patients with KOA. The primary efficacy analysis will follow the intention-to-treat (ITT) principle and will include all randomized participants who received at least one dose of the investigational product and underwent at least one post-baseline efficacy assessment. Participants will be analyzed according to their originally assigned groups regardless of treatment adherence or protocol deviations. Missing data for the primary and secondary outcomes will be handled using multiple imputation under the missing-at-random assumption. Sensitivity analyses will also be performed to evaluate the robustness of the findings. The per-protocol (PP) population, comprising participants who complete the 12-week intervention with adequate compliance and without major protocol deviations, will be used for sensitivity analyses. If the ITT and PP analyses yield different results, the ITT results will be considered primary and the PP analyses will be used for supplemental interpretation.

For the primary endpoint, the change in K-WOMAC scores from baseline to week 12 will be summarized using means and standard deviations and compared between the groups using independent *t*-tests. Repeated-measures analysis of variance (RM-ANOVA) will be used to assess the treatment effects over time and the interaction between group and time. The assumptions of repeated-measures analysis, including sphericity, will be assessed, and if violated, appropriate corrections such as the Greenhouse-Geisser adjustment will be applied. Although mixed-effects models may provide greater flexibility in handling missing data, RM-ANOVA was selected for consistency with the primary analytical framework. The same statistical approach will be applied to secondary continuous endpoints such as changes in pain visual analog scale (VAS) and EQ-5D-5L index scores. Categorical variables, such as the proportion of participants reporting adverse events or using rescue medications, will be analyzed using the chi-square test or Fisher's exact test. To adjust for potential confounders, analysis of covariance (ANCOVA) will be performed when appropriate, adjusting for baseline values and relevant covariates such as rescue medication use.

The safety analyses will include all participants who receive at least one dose of the investigational product. The incidence of adverse events will be compared between the groups using chi-square or Fisher's exact tests. Laboratory parameters, vital signs, and ECG findings will be analyzed using appropriate statistical methods based on data type and distribution. Descriptive statistics will be presented for continuous safety variables, and intergroup comparisons will be made using independent *t*-tests or non-parametric equivalents, while categorical safety outcomes will be analyzed using McNemar's tests or exact tests.

Economic evaluation will be performed from both healthcare system and societal perspectives, incorporating direct medical costs, non-medical costs, and indirect costs such as productivity loss. Incremental cost-utility ratios (ICURs) will be calculated based on the differences in costs and QALYs between the groups, with QALYs derived from EQ-5D-5L utility scores. Sensitivity analyses will be conducted to assess the robustness of the results using deterministic methods across plausible parameter ranges.[9]

# Discussion

GMDGHT is a long-standing Korean herbal prescription used to treat wind-dampness syndromes, including pain and stiffness associated with degenerative KOA. Laboratory data showing anti-inflammatory, analgesic, and immunomodulatory actions—such as reduced IgG/IgM production and suppression of NLRP3/NF-κB and Notch-1 signaling—lend biological plausibility to these traditional claims. Nevertheless, the clinical evidence remains confined to preclinical experiments, case reports, and uncontrolled series. Although GMDGHT has been used in routine clinical practice, such observational experience does not provide definitive evidence of its efficacy or safety. This study protocol has therefore been designed to address this gap through a randomized controlled trial.

The trial's methodological design directly addressed the key threats to validity. Multicenter recruitment enhances generalizability, whereas block randomization with allocation concealment limits the selection bias. Identical placebo granules uphold double-blinding, and independent assessors reduce the risk of detection bias. By situating the primary outcome on the K-WOMAC and adopting an ITT analysis, we preserved both clinical relevance and statistical integrity. The inclusion of a follow-up phase and cost-effectiveness evaluation further broadened the scope, allowing the study to capture sustained benefits, safety signals, and economic impacts in a single framework. Importantly, obtaining Investigational New Drug (IND) approval and producing GMP-grade granules ensures pharmaceutical consistency and regulatory oversight, which have been largely absent in previous herbal trials.

Despite its strengths, the limitations of this study warrant further investigation. Additionally, the restriction on concomitant use of NSAIDs and other analgesics may limit the generalizability of the findings, as patients with more severe symptoms may be less likely to participate. As data collection has not yet begun, no inference can be drawn regarding the clinical effectiveness or adverse event profile of GMDGHT. The 12-week treatment duration followed by a 12-week observation period may be insufficient to detect long-term structural changes or prevent relapse. Furthermore, the 24-week time horizon may be insufficient to fully capture long-term cost-utility outcomes in a chronic condition such as KOA. Eligibility criteria that restrict enrolment to adults aged 40–70 years with Kellgren–Lawrence grades I–III inevitably limit the applicability of future findings to older patients or those with end-stage disease. Finally, even under GMP conditions, batch-to-batch phytochemical variation, which is a reality in botanical products, cannot be eliminated entirely.

Notwithstanding these constraints, the protocol lays a transparent foundation for what will be the first IND-approved, randomized, placebo-controlled trial of GMDGHT for KOA. By pre-specifying the study procedures, endpoints, and analytical plan, we minimized selective reporting and analytical flexibility. Upon completion, the trial will clarify whether GMDGHT offers a safe, effective, and cost-effective therapeutic option for degenerative KOA and whether its traditional use should be reconsidered in light of contemporary clinical standards.

## Conclusion

This protocol will establish a rigorously designed, IND-approved, multicenter, double-blind RCT to determine whether GMDGHT is an effective, safe, and cost-effective treatment option for KOA.

## Funding

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: RS-2020-KH087677).

## Disclosure

The author(s) report no conflicts of interest in this work.

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