Efficacy Test of Curcuminoid Standardized Turmeric Capsules to Improving Inflammatory Biomarkers in Osteoarthritis Genu

Investigator
Srinalesti Mahanani
Nyoman Kertia
Desi Natalia Trijayanti Idris
Erlin Kurnia

KEDIRI BAPTIST HEALTH SCIENCE COLLEGE
INDONESIA

Table of contents

Protocol summary

Unique Protocol ID	055/20/VI/EC/KEPK-3/STIKES RSBK/2025
Title	Efficacy Test of Curcuminoid Standardized Turmeric Capsules to Improving Inflammatory Biomarkers in Osteoarthritis Genu
Brief title	Efficacy Test of Curcuminoid Standardized Turmeric Capsules to Improving Biomarkers in Osteoarthritis Genu
Sponsor and Clinical Phase	Ministry of Higher Education Science and Technology
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Evaluate the efficacy, safety, and tolerability of standardized curcuminoid from turmeric extract to TNF-Alpha, Interleukin-1 and CRP in elderly patients with Osteoarthritis Genu.
Primary Objective(s)	To determine the effectiveness of curcuminoid as measured by changes from baseline (BL) in TNF-Alpha, Interleukin-1 and CRP in the blood to placebo after three weeks of treatment in elderly patients with Osteoarthritis
Secondary Objectives	To evaluate the effect of acupressure and standardized curcuminoid from turmeric extract *vs* placebo at three weeks : Knee pain as measured by the VAS score
Study design	Randomized controlled trial, double-blind to assess efficacy, tolerability, and safety curcuminoid versus placebo. Patients can be pre-screened for specific x-ray and laboratory parameters. Eligible subjects will enter the washout for one week following a screening visit. After the washout period, eligible subjects will be randomized and treated for three weeks. The total duration of the study is up to 5 weeks.
Population	Approximately 60 female and male patients ≥ 65 years old
Key Inclusion criteria	• Clinical diagnosis of Osteoarthritis, which was confirmed by physical examination and X-rays • Experience pain with a Numeric Rating scale of 1-7 • Must be able to swallow capsules • Must be able to carry out mobility without assistance or with minimal assistance

Key Exclusion criteria	• Parkinson's disease • Dementia disease • Psychosis disease • Fractures • Joint dislocations • Cancer • Rheumatic diseases other than Osteoarthritis (rheumatoid arthritis) • Undergoing joint replacement therapy. • Analgesic dependent disease
Study treatment	• Combination of Acupressure and Curcuminoid from turmeric extract • Placebo
Efficacy assessments	• TNF-Alpha • Interleukin-1 • C-Reactive Protein
Key safety assessment	• Physical examination • Vital signs • Monitoring of laboratory markers in blood
Others assessment	• Knee pain
Data analysis	The primary efficacy variable is the number of TNF-Alpha, Interleukin-1 and CRP in blood, collected at Week 4 to BL (i.e., change from BL in the number of Leukocytes at Week 4). It will be analyzed using the Wilcoxon signed-rank test or paired t-test and the Mann-Whitney U test or independent t-test. The significance level will be set at 0.05. All outcome measures will be recorded at baseline and after two weeks of intervention
Keywords	Osteoarthritis, curcuminoid, randomized control trial, TNF-Alpha, Interleukin-1

1 Introduction

1.1 Background

One of the degeneration processes that occurs in the elderly is the musculoskeletal system. These deteriorations include bone loss and decreased joint fluid volume exacerbated by bearing the body's weight. This deterioration causes elderly people to experience pain. The experience of prolonged pain in Osteoarthritis patients becomes a " Breakpoint," which centers on the experience/process of living with unremitting pain, limitations in mobility, leisure, and social activities, and the resulting consequences for the patient's physical and psychological well-being. The breakpoint experienced by Osteoarthritis patients is the turning point for changes in the quality of life in Osteoarthritis. Popular alternative therapies include herbal therapy, therapeutic touch, relaxation techniques, music therapy, acupuncture, and acupressure. One of the therapies very close to the community, especially the Javanese, is acupressure, a further development of massage. Until now, massage is an action that people often do independently and can psychologically make patients feel comfortable, but research needs to continue to be carried out to ensure its effectiveness.

Pain in Osteoarthritis patients affects many areas of quality of life, such as physical function, emotional behavior, and mental health. Osteoarthritis-related pain is a major factor in poor quality of life. The most common pharmacological treatment to control pain is using non-steroidal anti-inflammatory drugs (NSAIDs), but these drugs risk causing side effects. Limitations associated with pharmacologic treatment result in patients choosing commonly available alternative therapies for pain management. Popular alternative therapies include herbal therapy, therapeutic touch, relaxation techniques, music therapy, acupuncture, and acupressure. Unlike the use of drugs, this alternative therapy does not produce dangerous side effects. (Li et al., 2018)

Research on the effectiveness of herbal therapy on inflammatory osteoarthritis patients was conducted in Indonesia by Kertia in 2009 on 80 sufferers with the result that administration of turmeric rhizome extract curcuminoids significantly suppressed the activity of synovial fluid monocytes to secrete COX-2 and ROI, reduced leukocyte numbers and fluid MDA levels. Synovia reduces OA joint pain, with an ability that is not significantly different compared to diclofenac sodium therapy 3x25 mg per day (Kertia, 2009). Furthermore, the development of herbal therapy for Osteoarthritis continued with research by Bertorio (Bertorio, 2017) which proved that the combination of ginger, ginger, soybean and shrimp shell extracts provided significant results in reducing joint pain, stiffness and physical disability which were evaluated based on the Western Ontario and McMaster values. Universities Osteoarthritis Index (WOMAC) did not show a significant difference when compared with meloxicam.

Research that has been carried out to evaluate the effectiveness of acupressure therapy for the pain of Osteoarthritis patients was also carried out in several countries, including by Alinaghizadeh on 40 Osteoarthritis patients who were divided into two groups (intervention and control). In the intervention group, acupressure therapy was given for 5 days for 30 minutes each time. The results showed that the average pain score in the intervention group decreased significantly from 5.89 at the beginning to 4.11 at the end of the study, while the pain score did not change substantially in the control group. These findings remained consistent after age, weight, and pretreatment covariates were adjusted. This study supports the evidence that Acupressure therapy provides an effective option for short-term knee pain relief in patients with knee Osteoarthritis. (Maryam Alinaghizadeh et al., 2021). In line with the results of Alinaghizadeh's research, there was research conducted by Akbarnezhad (Akbarnezhad et al., 2019) which was conducted on 51 elderly with Osteoarthritis divided into 3 groups (acupressure intervention, placebo and control). This study revealed that respondents who received acupressure therapy for 3-4 weeks with the duration of each therapy being 10-15 minutes,

showed a significant reduction in the total WOMAC index, pain and physical dysfunction.

So far, no research has been combining standardized curcuminoid turmeric extract therapy with acupressure for inflammation and pain in osteoarthritis patients. More clinical trials with appropriate methodology are needed to confirm the effectiveness of standardized turmeric extract, curcuminoids and acupressure to treat physical problems in osteoarthritis patients.

1.2 Purpose

To investigate the efficacy of standardized curcuminoids from turmeric extract to TNF-Alpha, Interleukin-1 and CRP in the blood and pain in elderly patient with Osteoarthritis Genu.

2 Study objectives and endpoints

2.1 Primary objective

To determine the effectiveness of combination two regimens (acupressure and curcuminoid) as measured by changes from baseline (BL) in TNF-Alpha, Interleukin-1 and CRP in blood to placebo after 3 weeks of treatment in elderly patients with Osteoarthritis

2.2 Secondary objectives

To evaluate the effect of acupressure and standardized curcuminoid from turmeric extract vs placebo at 3 weeks is Knee Pain that were measured by VAS

3 Investigational plan

3.1 Study design

Randomized controlled trial, we will conduct a 2-arm, double-blind (patient and investigational blinded) to assess efficacy, tolerability and safety curcuminoid versus placebo.

Pre-Screening:

Patients can be pre-screened for specific x-ray and laboratory parameters. Following a screening visit, eligible subjects will enter the washout. After the washout period, eligible subjects will be randomized and treated for 3 weeks. The total duration of the study is up to 5 weeks.

3.2 Study setting and source population

Eligible participants were individuals recruited from communities covered by government-owned primary care hospitals who consulted a rheumatology subspecialist physician with symptoms of pain and discomfort around the knee.
Participants will be recruited from June 2025 to September 2025. An informed consent form will be provided to participants in their local language to gain credibility. Codes will be assigned to ensure confidentiality for data collection, with only the primary researcher having access to the participant codes for each group. Participants providing their consent will be further screened for eligibility.

4 Population

The study population will consist of male and female patients (≥65 years old) with Osteoarthritis (Osteoarthritis with knee joint pain, knee joint stiffness in the morning less than 30 minutes, Crepitus, deformity, joint swelling (right and left asymmetrical), Other signs of inflammation (a feeling of even warmth and reddish color). The goal is to randomize a total of approximately 60 patients. Since a 25% screening failure rate and a 20% washout failure rate is expected,

approximately 100 patients will be screened.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Clinical diagnosis of Osteoarthritis which confirmed by physical examination and x-rays
2. Experience pain with a Numeric Rating scale of 1-7
3. Must be able to swallow capsules
4. Must be able to carry out mobility without assistance or with minimal assistance

4.2 Exclusion criteria

Patients fulfilling the following criteria are not eligible for inclusion in this study. The investigator may apply no additional exclusions to ensure the study population represents all eligible patients.

1. Parkinson's disease
2. Dementia disease
3. Psychosis disease
4. Fractures
5. Joint dislocations
6. Cancer
7. Rheumatic diseases other than Osteoarthritis (rheumatoid arthritis)
8. Undergoing joint replacement therapy.
9. Analgesic dependent disease

4.3 Eligibility test procedure

Radiographs will be used to assess participants for Osteoarthritis using the Kellgren and Lawrence criteria which divide Osteoarthritis from mild to severe. It should be remembered that at the beginning of the disease, the radiographic appearance of the joint still looks normal. According to Kellgren and Lawrence, radiologically, Osteoarthritis is classified as follows:

1) Grade 0: Normal, no signs of Osteoarthritis

2) Grade 1: Doubtful, without osteophytes, doubtful joint narrowing

3) Grade 2: Minimal, few osteophytes on the tibia and patella and the joint surface is asymmetrically narrowed.

4) Grade 3: Moderate, moderate osteophytes are in several places, the joint surface is narrowed, and subchondral sclerosis appears.

5) Grade 4: Severe, presence of large osteophytes, complete narrowing of the joint surface, severe subchondral sclerosis, and joint surface damage.

The Mini Mental State Examination (MMSE) test will assess the patient's cognitive abilities, whichi is essential to ensure that patients can understand the treatment and outcome measurement process instructions.

5 Randomization, allocation and blinding

60 eligible participants will be randomized to the group with curcuminoid capsules (C; group 1) or the group with placebo (P; group 2) via lottery randomization. After that subjects will be randomly allocated to C and P group. The schematic CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study protocol is presented in Figure 1—Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study.

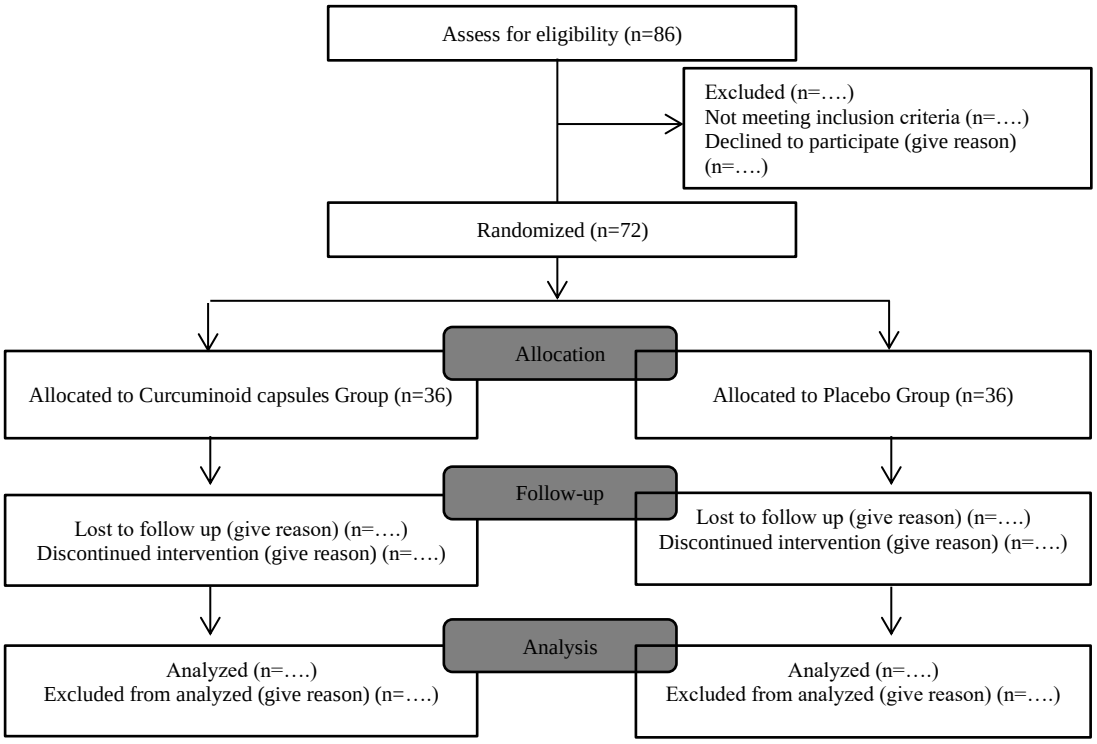

Figure 1. Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study

The therapist will determine baseline characteristics for every participant through a standardized assessment form. During the baseline measurement, the following characteristics will be recorded: sex, age, body mass, pain characteristic, history of disease and medication use. The participant's participation schedule will be determined according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement Figure 2. The primary and secondary outcome measures will be recorded before providing the intervention.

		STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**			
TIMEPOINT**		**0**	***1st week***	***2nd week***	***3rd week***	***1st day***	***1st week***	***2nd week***	***Post 3rd week***
ENROLMENT:									
Eligibility screen	X								

Informed consent	X								
[Radiography and MMSE Test]	X								
Allocation		X							
INTERVENTIONS:									
[C Therapy]			X	X	X				
[P Therapy]			X	X	X				
ASSESSMENTS:									
[Demographic Details]	X								
[TNF-Alpha]						X			X
[Interleukin-1]						X			X
[C-Reactive Protein]						X			X
[Knee Pain]						X	X	X	X

Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommended schedule for participation.

6 Intervention

After the standardized assessments and baseline measurements, the intervention will be conducted. Participants will be randomly assigned to the C group or the P group. Each participant will be exposed to taking Curcuminoid capsules three times a day for 21 days. Participants will not be allowed to take any medication routinely during this time except for antihypertensive agents, thyroid medications, and antidiabetic drugs. To help participants adhere to the interventions, reminder messages will be sent before each session visit.

The patient is observed for a local twitch response. The patient is asked to report any abnormal sensations or discomfort during intervention.

The sponsor will provide double-blind study medication for Curcuminoid and Placebo

Preparation of standardized curcuminoid turmeric extract. Samples were made from extracted turmeric and then optimized. The capsule formulation is made from turmeric rhizome extract which contains 30 mg of curcuminoids per capsule. In the study, standardized curcuminoid turmeric extract was given in capsules at 30 mg 3 times a day for 3 weeks.

7 Outcomes

All outcome measures will be assessed at baseline and after 3 weeks of intervention.

Primary Outcomes measures

1) Secretion of the TNF-Alpha

TNF alpha is a cytokine, a protein that plays a role in the immune system and inflammation. TNF alpha is produced by various types of cells, particularly activated macrophages, and plays a role in various biological processes such as inflammation and immunity against infection.

The cytokine TNF alpha is an essential mediator in increasing the inflammatory response, which can be detected in the blood plasma of patients with Osteoarthritis. The TNF alpha examination was conducted using the Enzyme Linked Immunosorbent Assay (ELISA) method on blood plasma.

2) Secretion of Interleukin-1

Interleukin-1 is a pro-inflammatory cytokine that plays a key role in immune and inflammatory responses, produced primarily by macrophages. IL-1 can cause fever, increase blood vessel permeability, and trigger bone and cartilage damage.

The cytokine Interleukin-1 is an essential mediator in increasing the inflammatory response, which can be detected in the blood plasma of patients with Osteoarthritis. The Interleukin-1 examination was conducted using the Enzyme Linked Immunosorbent Assay (ELISA) method on blood plasma

3) Secretion of C-Reactive Protein

C-reactive protein (CRP) is a blood marker for inflammation in the body, produced by the liver in response to infection, injury, or autoimmune conditions. A simple blood test measures CRP levels, with higher concentrations indicating greater inflammation.

C-reactive protein (CRP) is measured with a blood test to detect and monitor inflammation in your body. A blood sample is taken from a vein and analyzed in a laboratory to determine the CRP level. The results are reported in milligrams per liter (mg/L), and higher than normal levels indicate inflammation that may be caused by infection, injury, or a chronic condition.

Secondary outcomes

The effectiveness of therapy is the ability of the therapy regimen given to suppress several other expected output indicators. Other output indicators were measured before starting therapy and after 3 weeks of therapy is knee pain as measured by the VAS score

8 Statistical Issues

Sample size

The following formula estimates sample size

$$N = \frac{2\sigma^2(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu 1 - \mu 2)^2}$$

where N is the sample size required in both groups, s is the standard deviation of the primary outcome. This research has a confidence level (1- a) of 95%, so the value obtained is a = 5%. Therefore, the research hypothesis is unidirectional, so the magnitude of Z1-a = 1.96. The research's power (1-β) was also set at 80%, so the value of β = 20%, then the amount of Z1-β = 0.842. Previous research analyzed changes in leukocytes in subjects treated with curcuminoid therapy from turmeric extract 30 mg 3 times a day for 14 days, amounting to 30.00 ± 5.10 and meloxicam 1 x 15 mg per day, obtained the mean delta value of leukocytes in the control group was 164.1+50.91 and the treatment group was 174.27+78.93.

$$N = \frac{2\sigma^2(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu 1 - \mu 2)^2}$$

$$= \frac{2(14{,}01)^2(1{,}96+0{,}842)^2}{(174{,}27-164{,}1)^2}$$

$$N = \frac{392{,}5602\ (2{,}802)^2}{(174{,}27-164{,}1)^2}$$

$$N = \frac{3082{,}07}{103{,}4289}$$

N = 29,79 – (30 people)

The total respondents required in the 2 groups is 60 people. Considering a dropout rate of 20%, the sample size should be increased to 36 each group.

9 Protection of Human Subjects and Assessment of Safety

9.1 Protection of participants

The ethics research committee has approved the study protocol registered with the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) (project number KE-FK-0674-EC-2023). The study will be conducted according to Indonesia's 2021 National Health Research and Development Ethical Guidelines and Standards by the Health Research and Development Ethics Committee and the Helsinki Declaration, revised in 2013.

9.2 Adverse events

We will look for any adverse events that might occur during each administration of CA Therapy, including increased soreness, pain, numbness, and tingling. Any adverse event that is life-threatening or related to significant disability will be reported to the ethics research committee of the institution.

9.3 Data analysis

The secondary researcher will analyze the data collected. Descriptive statistics will be used to evaluate the baseline characteristics of participants. The normality of the collected data will be established using the Shapiro–Wilk test. Based on data normality, descriptive statistics will be expressed as mean ± standard deviation or median (interquartile range). Within-group comparisons will be conducted using the Wilcoxon signed-rank test or a paired t-test. Similarly, the Mann–Whitney U test or an independent t-test will be used for between-group comparisons. The level of significance will be set at 0.05.

9.4 Data management

Data collected will be kept confidential throughout the study and discarded after 5 years. Initial data documentation will be performed through printed data-collection forms, which will later be managed and transcribed into electronic format and stored on a desktop computer without an internet connection (to help prevent unauthorized data access) for further analysis. The chair of the student project committee of the institute will oversee data

10. Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported by the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including Indonesia's 2021 National Health Research and Development Ethical Guidelines and Standards by the Health Research and Development Ethics Committee and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the pre-screening or the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the pre-screening and the study, as applicable, to the extent possible given his/her understanding. If the patient can do so, he/she must indicate assent by signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any pre-screening or study- specific procedures (e.g. pre-screening assessments/all of the procedures described in the protocol). The patient source documents must document the process of obtaining informed consent.

Novartis will provide to investigators in separate documents proposed pre-screening and study informed consent forms that comply with the ICH GCP guideline and regulatory requirements and are considered appropriate for pre-screening and participation in the study. Novartis must agree to any changes to the proposed consent forms suggested by the investigator before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form(s), consent form updates, patient recruitment procedures (e.g., advertisements) and any

other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study by these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, Quality Assurance representatives, designated agents of IRBs/IECs, and regulatory authorities as required. If a regulatory authority requests an inspection of the clinical site, the investigator must inform IRBs/IECs immediately that this request has been made.

10.4 Publication of study protocol and results

The critical design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the trial results will be either submitted for publication and posted in a publicly accessible database of clinical trial results.

11. Protocol adherence

This protocol defines the study objectives, procedures, and data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research-related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by health authorities where required, and the IRB/IEC prior to implementation. Only amendments intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol..

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