Effect of a Combination of Curcuminoid Standardized Turmeric Extract with Acupressure on Inflammatory Markers, Endorphins and Quality of Life Elderly with Osteoarthritis Genu

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Protocol summary

Unique Protocol ID	KE/FK/0674/EC/2023
Title	Effect of a Combination of Curcuminoid Standardized Turmeric Extract with Acupressure on Inflammatory Markers, Endorphins and Quality of Life Elderly with Osteoarthritis Genu
Brief title	Combination of Curcuminoid With Acupressure for Inflammationand Pain in the Elderly With Osteoarthritis Genu
Sponsor and Clinical Phase	Gadjah Mada University, Phase 2a
Investigation type	Drug and acupressure
Study type	Interventional
Purpose and rationale	Evaluate the efficacy, safety and tolerability of acupressure and standardized curcuminoid from turmeric extract to inflammatory markers, endorphin hormones in the blood and quality of life in elderly patient with Osteoarthritis Genu
Primary Objective(s)	To determine the effectiveness of combination two regimens (acupressure and curcuminoid) as measured by changes from baseline (BL) in Leukocytes, Neutrophil Leukocyte Ratio, Blood Sedimentation Rate, Pain, secretion of COX-2 and Endorphin hormones in blood to placebo after 3 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 3 weeks : • Knee pain as measured by the VAS score • Joint stiffness and joint functional ability are assessed by the WOMAC score • The independence of the elderly as assessed by the Barthel Index • Quality of Life were measured by Respondents' satisfaction in carrying out daily activities based on indicators on the KOOS instrument
Study design	Randomized controlled trial, double-blind to assess efficacy, tolerability and safety combination of acupressure and curcuminoid versus placebo. Patients can be pre-screened for certain x-ray and laboratory parameters. Following a screening visit, eligible subjects will enter the wash-out for 1 week. After the wash-out period, eligible subjects will be randomized and treated for 3 weeks. The total duration of the study is up to 5 weeks
Population	Approximately 70 female and male patients ≥ 65 years old
Key Inclusion criteria	• Clinical diagnosis of osteoarthritis which 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 • New bone fractures • Joint dislocations • Cancer • Rrheumatic 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	• Leukocytes • Neutrophil Leukocyte Ratio • Blood Sedimentation Rate • Pain • Secretion of COX-2 in blood • Secretion of Endorphin hormones in blood
Key safety assessment	• Physical examination • Vital signs • Monitoring of laboratory markers in blood
Others assessment	• Quality of Life
Data analysis	The primary efficacy variable is the number of Leukocytes (mcL), Neutrophil Leukocyte Ratio, Secretion of COX-2 in blood, Secretion of Endorphin hormones 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 wilcoxon signed-rank test or paired t test and 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 2 weeks of intervention
Keywords	Osteoarthritis, curcuminoid, acupressure, randomized control trial

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 a decrease in joint fluid volume which is exacerbated by bearing the weight of the body. 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 quality of life in Osteoarthritis. Popular alternative therapies include herbal therapy, therapeutic touch, relaxation techniques, music therapy, acupuncture, and acupressure. One of the therapies that is very close to the community, especially the Javanese, is acupressure, which is 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 the use of non-steroidal anti-inflammatory drugs (NSAIDs), but these drugs carry the risk of 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. This alternative therapy, unlike the use of drugs, 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 and 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 Osteoathritis 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) and 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 with a duration of 30 minutes each time. The results showed that the average pain score in the intervention group decreased significantly from 5.89 at the beginning of the study 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 adjusting for age, weight, and pretreatment covariates. 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, there has been no research 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 acupressure and standardized curcuminoids from turmeric extract to inflammatory markers, endorphin hormones in the blood and quality of life 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 Leukocytes, Neutrophil Leukocyte Ratio, Blood Sedimentation Rate, Pain, secretion of COX-2 and Endorphin hormones 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 Quality of Life that were measured by Respondents' satisfaction in carrying out daily activities based on indicators on the *Knee injury and Osteoartritis Outcome Score (*KOOS) instrument

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 combination of acupressure and curcuminoid versus placebo.

Pre-Screening:

Patients can be pre-screened for certain x-ray and laboratory parameters. Following a screening visit, eligible subjects will enter the wash-out. After the wash-out 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 Agustus 2023 to September 2023. 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 70 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 any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Parkinson's disease
2. Dementia disease
3. Psychosis disease
4. New bone fractures
5. Joint dislocations
6. Cancer
7. Rrheumatic 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, there are moderate osteophytes 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.

Mini Mental State Examination (MMSE) test will be used to assess the patient's cognitive abilities. This is important to ensure that patients can understand the instructions in the treatment process and the outcome measurement process.

5 Randomization, allocation and blinding

A total of 70 eligible participants will be randomized to the group with curcuminoids capsules and acupressure (C+A; group 1) or the group with placebo and sham acupressure (P+S; group 2) via lottery randomization. Thereafter subjects will be randomly allocated to C+A and P+S 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.

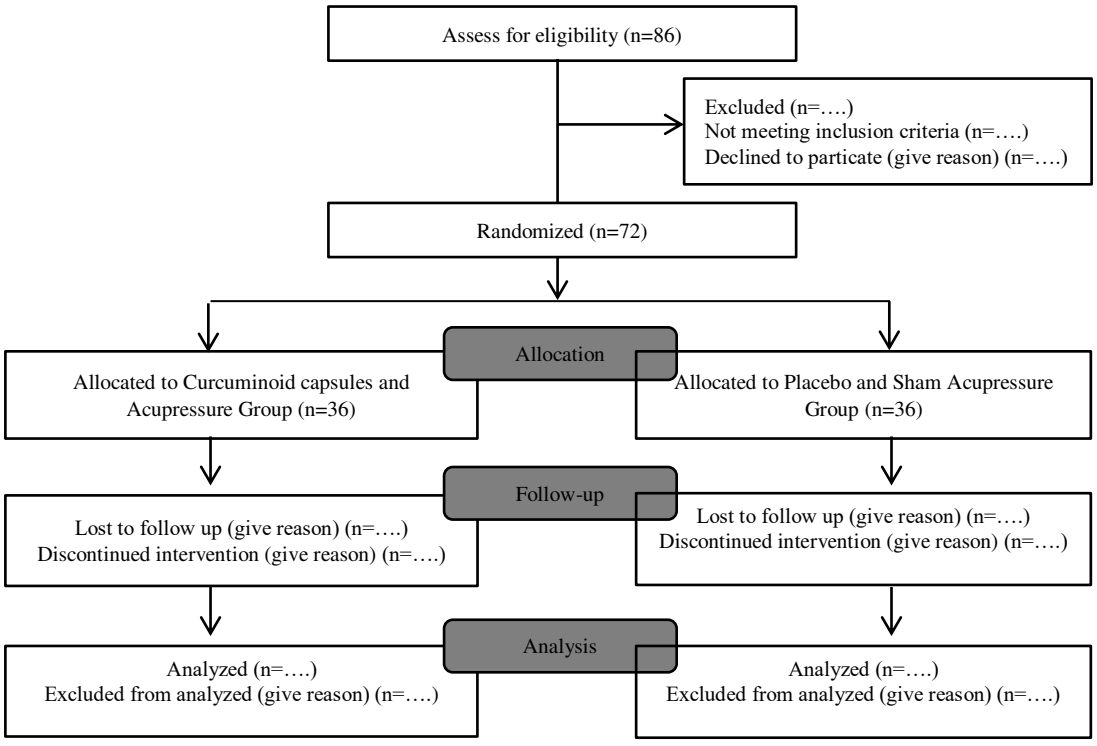


Figure 1. Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study

Determination of baseline characteristics for every participant will be done by the therapist 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.

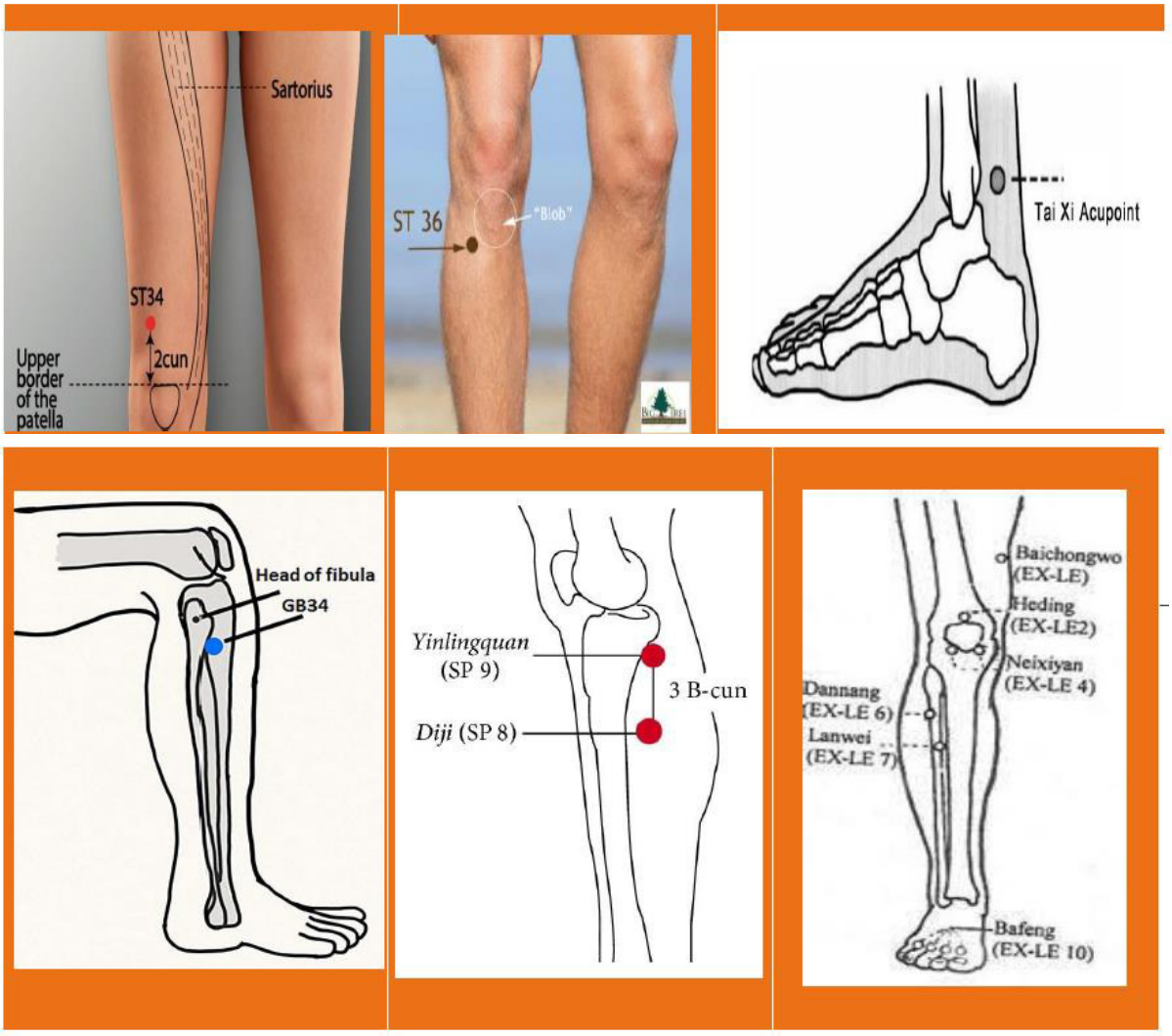
		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation			Close-out			
TIMEPOINT**		0	*1st week*	*2nd week*	*3rd week*	*1st day*	*1st week*	*2nd week*	*Post 3rd week*
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
[Radiography and MMSE Test]	X								
Allocation		X							
INTERVENTIONS:									
[C+A Therapy]			X	X	X				
[P+S Therapy]			X	X	X				
ASSESSMENTS:									
[Demographic Details]	X								
[Inflammatory Marker]						X			X
[Endorphine]						X			X
[Quality of Life]						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 CA group or the PS group. For Acupressure Therapy and Sham Acupressure, each participant will be exposed to 3 therapy sessions per week of 20 minutes for 3 consecutive weeks. 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. For Curcuminoid capsules and placebo, Each participant will be exposed to taking capsules three times a day for 21 days.

Acupressure to perform CA, the patient is put in the supine position with legs straight. Prepare tools and materials such as a seat (or bed), warm water, olive oil, wet & dry tissue, towels. The therapist washes his hands, the client sits in a comfortable position. Teach patients breathing relaxation techniques to use during therapy. Give patients the opportunity to pray according to their respective beliefs. Make sure the client is relaxed and comfortable. Help remove the client's clothing or accessories that may hinder the acupressure action being performed, if necessary. Perform a client pain assessment. Wipe the client on the parts to be massaged with warm water that has been treated with a disinfectant solution using a small towel. Dry with a clean towel. Use cream or oil, do a warming massage with basic massage techniques, choose according to the client's condition (rubbing, squeezing, pressing) and stretching the patient's feet. Acupressure massage points are performed at ST34, ST36, Tai Xi Acupoint, GB34, SP 9, SP 8, EX-LE, EX-LE3, EX-LE4, EX-LE6, EX-LE7, EX-LE10



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

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

Preparation of standardized curcuminoid turmeric extract preparations. 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 a concentration of 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) Inflammatory Markers

Inflammation markers are carried out by measuring leukocyte numbers and the Neutrophil Lymphocyte Ratio. The examination is carried out using a complete blood test using a Hematology Analyzer, which is a laboratory tool used to measure and count the number of blood cells. The blood samples are mixed using a mixture of reagents to create a process called hemolyzing. This process will be divided into several purposes, to measure leukocytes, neutrophils, platelets and erythrocytes.

2) Secretion of the COX-2 hormone

The enzyme cycloxygenase-2 (COX-2) is an important mediator in increasing the inflammatory response. In the blood plasma of patients with osteoarthritis, the COX-2 enzyme can be detected. The COX-2 hormone examination was carried out using the Enzyme Linked Immunosorbent Assay (ELISA) method on blood plasma.

3) Secretion of endorphin hormones

Endorphins, in this case beta endorphin, are hormones released by the pituitary gland in response to stress or pain, which are also secreted in blood plasma. Endorphin hormone levels in the blood were measured before starting therapy and after 3 weeks of therapy.

Endorphin hormone examination is carried out using the Enzyme Linked Immunosorbent Assay (ELISA) method on blood plasma that has been incubated at room temperature for 10-20 minutes, then the tube will be centrifuged for 20 minutes at a speed of 2000-3000 rpm.

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

1) Knee pain as measured by the VAS score

2) Joint stiffness and joint functional ability are assessed by the WOMAC score.

WOMAC is a questionnaire developed by Bellamy (Bellamy et al., 1988) and continues to be developed to measure the functional abilities of patients with knee osteoarthritis. The WOMAC instrument has been translated into Indonesian and has been tested for validity by Karsten (Karsten et al., 2019) with the results of the Crohnbach's Alpha coefficient of 0.966, indicating that there is relatively high internal consistency and is highly correlated, meaning that the WOMAC questionnaire in Indonesian is correct. validated and can be used by the Indonesian people. This questionnaire can evaluate 3 subscales, namely (1) pain (5 items), (2) stiffness (2 items) and (3)

physical function (17 items) by scoring on a 5-point ordinal scale. The details of the scores are (1) pain: score 0 "no pain", score 1 "mild pain", score 2 "moderate pain" score 3 "severe pain" and score 4 "very severe pain"; (2) stiff: score 0 "not stiff", score 1 "mildly stiff", score 2 "medium stiff", score 3 "extremely stiff" and score 4 "stiff to the point of locking"; (3) physical function: score 0 "not difficult", score 1 "somewhat difficult", score 2 "quite difficult", score 3 "very difficult" and score 4 "very difficult". Range of subscale scores for pain (0-20), stiffness (0-8) and physical function (0-68). The total score is obtained by adding up the scores of the 3 subscales, with a maximum score of 96. A higher WOMAC score indicates pain, stiffness and worse physical function. The total WOMAC score can be categorized into 3 groups, namely low risk (score ≤ 60), moderate risk (score 60-80) and high risk (score ≥ 81).

3) The independence of the elderly as assessed by the Barthel Index

The Barthel Index questionnaire was first developed in 1965 by Mahoney. Inventory of this instrument is held by The Maryland State Medical Society. Then in 2020, Pontansi (Pontung & et al, 2020) translated it into Indonesian and carried out a validity test with the result that inter-rater reliability was satisfactory.

In terms of content validity, the Indonesian version of the Barthel Index is acceptable. The construct validity test revealed two main factors, namely functional performance and physiological function.

4) Quality of Life assessed with KOOS

KOOS is an instrument to assess patient opinions about the condition of the knee and problems related to the knee. KOOS has been translated into Indonesian and tested for validity by Phatama (Phatama & et al, 2021) with Cronbach α results of 0.84 to 0.97 for all subscales, indicating adequate internal consistency. Test-retest reliability was excellent, with intraclass correlation coefficients ranging from 0.91 to 0.99 for all subscales. No significant differences were found in KOOS subscale responses between the first administration of the questionnaire and the second administration within 21 days. The Indonesian version of the KOOS was declared valid and reliable and therefore is an objective instrument for evaluating knee ligament injuries and knee osteoarthritis in the Indonesian population. KOOS can be used as a measurement of quality of life because it includes measurements of 5 subscales, namely (1) Symptoms; (2) Rigidity; (3) Pain; (4) Daily Activities; (4) Sports and Recreation Activities and (5) Knee-related Quality of Life. in circumstances one week prior is the time period considered when answering the question. Answer options are standard (Likert scale) and each question is scored from 0 to 4. Scores are normalized (a score of 100 indicates no symptoms and 0 indicates extreme symptoms).

8 Statistical Issues

Sample size

Sample size is estimated by the following formula

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

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. Power (1-β) in the research was also set at 80%, so that 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 orang)

This gives the total number required in the 2 groups. 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 study protocol has been approved by the ethics research committee 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 the presence of any adverse events that might occur during each administration of CA Therapy, which include 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 data collected will be analyzed by the secondary researcher. 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-groups comparisons. The level of significance will be set at 0.05.

9.4 Data management

Data collected will be kept confidential throughout the study duration and will be discarded after 5 years. Initial documentation of data 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. Data will be overseen by the chair of the student project committee of the institute

10. Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with 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 in 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/or the study, as applicable, to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally 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 process of obtaining informed consent must be documented in the patient source documents.

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 for participation in the study. Any changes to the proposed consent forms suggested by the investigator must be agreed to by Novartis 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 child bearing 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 in order 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 in accordance with 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 an inspection of the clinical site is requested by a regulatory authority, the investigator must inform IRBs/IECs immediately that this request has been made.

10.4 Publication of study protocol and results

The key 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 results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11. Protocol adherence

This protocol defines the study objectives, the study procedures and the 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 that are 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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EXPLANATION SHEET TO PROSPECTIVE SUBJECTS

We, the research team consisting of Srinalesti Mahanani, Nyoman Kertia, and Ema Madyaningrum, chaired by Srinalesti Mahanani from the Faculty's Doctoral Study Program Medicine, Public Health and Nursing Gadjah Mada University will conducted research entitled The Effect of a Combination of Standardized Turmeric Extracts Curcuminoids with Acupressure on Inflammatory Markers, Endorphins and Quality of Life Elderly with Osteoarthritis Genu.

This research aims to determine the effect of a combination of turmeric extract standardized curcuminoids with acupressure on leukocyte levels, ESR, NLR, endorphins and quality of life of elderly with genu osteoarthritis.

The research team invites fathers/mothers/relatives to take part in this research. This research requires around 72 research subjects, with a period of participation each subject approximately 4 weeks - 2 months.

A. Volunteering to participate in research

You are free to choose to participate in this research without any coercion. if you If you have decided to join, you are also free to withdraw/change mind at any time without being subject to any fines or sanctions.

If you are not willing to participate then you will still get treatment at Posyandu Padukuhan Tanjungsari, Sukoharjo Ngaglik Sleman Village in accordance with applicable procedures.

B. Research Procedures

If you are willing to participate in this research, you will be asked to sign This consent form is in two copies, one for you to keep, and one for you researcher. The next procedure is:

1. Mr/Mrs/Br will be interviewed by a doctor to ask: Name, age, history disease, history of drug use, history of allergies, smoking habits.
2. Mr/Mrs/Sdr will also be interviewed with several questions according to the questionnaire which exists. This interview aims to measure levels of anxiety and health your mentality.
3. Mr/Mrs/Sdr will undergo a physical examination by a doctor to check the status health

4. Mr/Mrs/Br will undergo an X-ray examination of the knee
5. If you use painkillers, you will be asked to
   Stop consuming for 1 week
6. One week later the research will begin. You will be asked to come together
   at the posyandu at 6.45 for further blood collection.
7. Blood sampling was carried out twice during the research period
   how to place a butterfly needle in a vein in the forearm.
   Blood collection is carried out using a butterfly needle that has been installed.
   The first collection is carried out before therapy is given in approximately one amount
   tablespoon, and the next intake is after the therapy is given
   about one tablespoon
8. This first blood draw is for laboratory examination regarding the condition
   blood and body hormones.
9. Blood collection is carried out by nurses who are accustomed to taking blood.
10. Because in this research there will be 2 groups, namely the group that
    given medication and therapy as well as groups who did not receive medication and therapy
    then Mr/Ms/Sdr will be divided into 2 groups randomly so that there are
    It is possible that the capsule given to you may not contain it
    medicinal ingredients. Respondents and researchers do not know which group they fall into, only
    only the therapist knows.
11. On the appointed day and for the next 21 days, Mr/Mrs/Br will be given
    The medicine is in capsule form which must be taken with water 3 times
    a day. And also Mr/Ms/Sdr will get a visit schedule for therapy
    acupressure. Mr/Ms/Sdr will be asked to come to the therapist's house according to the schedule.
12. This research will involve families to accompany respondents during the process
    research (the family will accompany the respondent in drinking herbal therapy, filling
    observation sheet for taking medication and accompanying when administering acupressure therapy as well
    report to researchers if unbearable pain occurs during the period
    study).
13. Researchers will involve posyandu cadres to alert patients and families
    taking medication and doing therapy, as well as researchers will create a system
    reminder to remind the family.

C. Obligations of research subjects

As research subjects, you are obliged to follow the rules or regulations research instructions as written above. If something is not clear, You can ask the researchers further questions. During the research, no permitted to take other medicines or herbal medicines other than those given by the researcher.

D. Risks and Side Effects and Their Management

Turmeric herbal therapy interventions and acupressure massage do not provide any side effects straight to you. During the research, researchers set up protective measures necessary if something undesirable happens. Protection provided by researchers is examination by a doctor and treatment in hospital.

E. Benefits

The direct benefit you get is that you get non-therapy pharmacological to treat pain and discomfort due to Osteoarthritis Genu as well useful for further treatment at home.

F. Confidentiality

All information relating to the identity of research subjects will be kept confidential and will only be known to researchers, research staff and auditors. The research results will be published without the identity of the research subjects.

G. Compensation

You will receive an X-ray examination to determine the condition knee joint and will receive therapy in accordance with the provisions of the study. Mr/Ms/Sdr will get tools for massage therapy (towel and oil). the next will be yours. After the research activities are completed, Mr./Ms./Br Those in the control group will receive herbal therapy and therapy acupressure according to that received by the treatment group.

H. Financing

All costs related to research will be borne by the researcher.

I. Additional Information

You are given the opportunity to ask anything that is not clear in connection with this research. If at any time side effects occur or If you need further explanation, you can contact Srinalesti Mahanani at No. Mobile phone. 085729006547.

You can also ask the Ethics Committee about research Medical and Health Research, Faculty of Medicine, UGM (Tel. 0274-588688, ext 17225 or +62811-2666-869; email: mhrec_fmugm@ugm.ac.id).

CONSENT TO PARTICIPATE IN RESEARCH

All these explanations have been conveyed to me and all my questions have been answered answered by the researcher. I understand that if I need an explanation, I can asked Srinalesti Mahanani.

By signing this form, I agree to take part in this research

Patient/subject signature: Date:

(Clear name :..... ..)

Witness signature:

(Clear name :..... ..)