# Clinical Trial Protocol
# Iranian Registry of Clinical Trials

31 May 2026

## The effect of Bromelain supplementation alone and in combination with Curcumin on disease symptoms and severity, inflammatory markers and oxidative stress in patients with Rheumatoid Arthritis

## Protocol summary

**Study aim**

The effect of Bromelain supplementation alone and in combination with Curcumin on disease symptoms and severity, inflammatory markers and oxidative stress in patients with Rheumatoid Arthritis

**Design**

A phase 3, randomized, triple-blind, controlled clinical trial conducted on 75 patients.

**Settings and conduct**

Blood samples will be collected twice from Rheumatoid Arthritis (RA) patients visiting Firoozgar Hospital who meet the inclusion criteria: once at baseline and once after the intervention, to assess the targeted factors.

**Participants/Inclusion and exclusion criteria**

Inclusion Criteria: 1. Willingness to participate and signing the informed consent form. 2. Age between 18 and 65 years. 3. Diagnosis of Rheumatoid Arthritis (RA) based on the American College of Rheumatology (ACR) criteria 4. Disease duration of at least two years. 5. No intake of dietary supplements (antioxidants, omega-3, etc.) in the past two months, except for routine supplements prescribed for Rheumatoid Arthritis (Vitamin D, Calcium, Vitamin A). 6. No history of diabetes, hypertension, acute cardiovascular diseases, thyroid disorders, kidney failure, or liver dysfunction based on the patient's medical history. 7. Stable medication regimen for at least one month before the study. 8. Not pregnant or breastfeeding 9. No use of contraceptive drugs. 10. No substance abuse. 11. Exclusion of individuals with allergies to pineapple, carrot, or fennel. 12. Exclusion of individuals taking anticoagulant medications.

**Intervention groups**

Three groups of 25 RA patients: Bromelain (200 mg), Bromelain + Curcumin (200 mg + 300 mg), and Placebo (Maltodextrin).

**Main outcome variables**

TAC, MDA, CRP, ESR, TNF-α, IFN-γ, IL-17, disease severity, number of painful joints, number of inflamed joints, number of joints with tenderness, pain level, DAS28, joint stiffness

## General information

**Reason for update**

**Acronym**

**IRCT registration information**

IRCT registration number: **IRCT20120415009472N29**
Registration date: **2025-03-15, 1403/12/25**
Registration timing: **prospective**

Last update: **2025-03-15, 1403/12/25**
Update count: **0**

**Registration date**

2025-03-15, 1403/12/25

**Registrant information**

**Name**

Naheed Aryaeian

**Name of organization / entity**

Iran University of Medical Sciences

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**Recruitment status**

**Recruitment complete**

**Funding source**

**Expected recruitment start date**

2025-04-21, 1404/02/01

**Expected recruitment end date**

2026-04-21, 1405/02/01

**Actual recruitment start date**
empty
**Actual recruitment end date**
empty
**Trial completion date**
empty

**Scientific title**
The effect of Bromelain supplementation alone and in combination with Curcumin on disease symptoms and severity, inflammatory markers and oxidative stress in patients with Rheumatoid Arthritis

**Public title**
The effect of bromelain and curcumin on rheumatoid arthritis
**Purpose**
Supportive
**Inclusion/Exclusion criteria**
**Inclusion criteria:**
Diagnosis of Rheumatoid Arthritis Based on American College of Rheumatology (ACR) Criteria(If there are at least four criteria for six weeks of the criteria 1- Morning dryness for at least one hour in three joints or more 2- Arthritis of three joint areas or more 3- Arthritis of the hand joints 4- Symmetric arthritis 5- Rheumatoid nodules 6- Positive rheumatoid factor 7- Typical radiographic changes in the wrist and hand) The duration of the disease should be at least two years. The patient expresses his / her consent to participate in the study
**Exclusion criteria:**
Taking supplements (omega 3, antioxidants, etc.) in the last two months Having any of the diseases of diabetes, hypertension, thyroid disorder and kidney failure and Liver dysfunction Changes in the amount of medication taken in the past month Pregnancy and lactation Taking contraceptives People who are allergic to pineapple, carrots, and fennel. People who take anticoagulant medications. Substance abuse
**Age**
From **18 years** old to **65 years** old
**Gender**
Both

**Phase**
3
**Groups that have been masked**

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data analyser
- Data and Safety Monitoring Board

**Sample size**
Target sample size: **75**
**Randomization (investigator's opinion)**
Randomized
**Randomization description**
In this study, samples will be selected based on availability, and randomization will be performed for group allocation. For randomization, a random list for three groups, each with a sample size of 25 participants, was generated using web-based software. The letters A, B, and C will be assigned to the numbers 1 to 3 using random number generation. The numbers 1 to 3 correspond to the three groups: Group 1 (Bromelain), Group 2 (Bromelain + Curcumin), and Group 3 (Placebo). Based on the order of patient visits, the type of intervention, represented by letters A, B, and C, will be assigned to each patient according to the sequential list generated by the random number software. Patient selection will initially be based on their visits, making it a convenience sample, but drug allocation will be randomized.
**Blinding (investigator's opinion)**
Triple blinded
**Blinding description**
This study is a triple-blind, placebo-controlled randomized clinical trial, meaning that the patient, the researcher, and the analysts performing the statistical analyses will remain unaware of the type of intervention until the analysis is completed. The pharmacist will attach labels A, B, and C to the medication packages, which will be provided to patients visiting the therapist according to the sequential list generated by the random number program. After the completion of the analysis and the review of the results, the pharmacist will be contacted to disclose the label assignments. This information will then be used in the preparation of the report and the manuscript, particularly in the findings, discussion, and conclusion sections.
**Placebo**
Used
**Assignment**
Parallel
**Other design features**

## Secondary Ids

empty

## Ethics committees

### 1

**Ethics committee**
**Name of ethics committee**
Research Ethics Committees of Iran University of Medical Sciences
**Street address**
Iran University of Medical Sciences Hemat Highway, Between Sheikh Fazlollah Nouri Highway and Shahid Chamran Highway, Next to Milad Tower, Tehran, Iran
**City**
Tehran
**Province**
Tehran
**Postal code**
1449614535
**Approval date**
2025-02-23, 1403/12/05
**Ethics committee reference number**
IR.IUMS.REC.1403.1051

## Health conditions studied

### 1

**Description of health condition studied**
Rheumatoid arthritis
**ICD-10 code**
M05
**ICD-10 code description**
Rheumatoid arthritis with rheumatoid factor

## Primary outcomes

### 1

**Description**
Tumour necrosis factor- α (TNF-α)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Enzyme-linked immunosorbent assay (ELISA)

### 2

**Description**
Total antioxidant capacity (TAC)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Chromatography

### 3

**Description**
Erythrocyte sedimentation rate (ESR)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Westergren method

### 4

**Description**
Malondialdehyde (MDA)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Chromatography

### 5

**Description**
Interferon gamma (IFN-γ)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Enzyme-linked immunosorbent assay (ELISA)

### 6

**Description**
Interleukin-17 (IL-17)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Enzyme-linked immunosorbent assay (ELISA)

### 7

**Description**
C-reactive protein (CRP)
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Immunoturbidometric method

### 8

**Description**
Disease activity score
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Formula DAS28

### 9

**Description**
Illness severity
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Physician global assessment

### 10

**Description**
Pain
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
Visual analogue scale

### 11

**Description**
Morning stiffness
**Timepoint**
Before the intervention and after the end of the intervention
**Method of measurement**
How long (minutes) it takes for the joint dryness to go away.

### 12

**Description**

Number of painful joints

**Timepoint**

Before the intervention and after the end of the intervention

**Method of measurement**

Doctor's examination

### 13

**Description**

Tender joint counts (TJC)

**Timepoint**

Before the intervention and after the end of the intervention

**Method of measurement**

Doctor's examination

### 14

**Description**

Swollen joint count

**Timepoint**

Before the intervention and after the end of the intervention

**Method of measurement**

Doctor's examination

## Secondary outcomes

### 1

**Description**

Dosage of drugs

**Timepoint**

Before the intervention and after the end of the intervention

**Method of measurement**

Questionnaire

## Intervention groups

### 1

**Description**

Intervention Group 1:A total of 25 participants in this group will receive bromelain, taking two 200 mg bromelain capsules daily (one with breakfast and one with lunch) for 12 weeks. The capsules will be provided by Salamat Parmon Amin (SPAmeda) Company.

**Category**

Treatment - Drugs

### 2

**Description**

Intervention Group 2:A total of 25 participants in this group will receive a combination of bromelain and curcumin, taking two capsules daily, each containing 200 mg of bromelain and 300 mg of curcumin (one with breakfast and one with lunch) for 12 weeks. The capsules will be provided by Salamat Parmon Amin (SPAmeda) Company.

**Category**

Treatment - Drugs

### 3

**Description**

Control Group:A total of 25 participants in this group will receive a placebo, taking two capsules daily containing maltodextrin (identical in appearance, color, smell, and taste to the intervention capsules but with no therapeutic effect), one with breakfast and one with lunch, for 12 weeks. The capsules will be provided by Salamat Parmon Amin (SPAmeda) Company.

**Category**

Placebo

## Recruitment centers

### 1

**Recruitment center**

**Name of recruitment center**

Firoozgar hospital

**Full name of responsible person**

Simin Almasi

**Street address**

Firouzgar Hospital, Be'afarain St., Valiasr Sq.

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firoozgarhospital1@gmail.com

## Sponsors / Funding sources

### 1

**Sponsor**

**Name of organization / entity**

Iran University of Medical Sciences

**Full name of responsible person**

Dr. Majid Safa

**Street address**

Vice-chancellor for Research, Iran University of Medical Sciences, Hammat Broadway

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**Grant name**

**Grant code / Reference number**

**Is the source of funding the same sponsor organization/entity?**
Yes
**Title of funding source**
Iran University of Medical Sciences
**Proportion provided by this source**
100
**Public or private sector**
Public
**Domestic or foreign origin**
Domestic
**Category of foreign source of funding**
*empty*
**Country of origin**
**Type of organization providing the funding**
Academic

## Person responsible for general inquiries

**Contact**
**Name of organization / entity**
Iran University of Medical Sciences
**Full name of responsible person**
Naheed Aryaeian
**Position**
Professor
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**Other areas of specialty/work**
Nutrition
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## Person responsible for updating data

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## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**
Undecided - It is not yet known if there will be a plan to make this available
**Study Protocol**
Yes - There is a plan to make this available
**Statistical Analysis Plan**
Yes - There is a plan to make this available
**Informed Consent Form**
Yes - There is a plan to make this available
**Clinical Study Report**
Yes - There is a plan to make this available
**Analytic Code**
Yes - There is a plan to make this available
**Data Dictionary**
Yes - There is a plan to make this available
**Title and more details about the data/document**
Only a section of the data, such as primary outcomes

information or the like, will be shared.

**When the data will become available and for how long**

Access period start 5 months after results publishing.

**To whom data/document is available**

The obtained data from current study will be available only for working researchers in academic and scientific institutions

**Under which criteria data/document could be used**

5 months after the publicized papers from this study, the obtained data will be available to the researchers for further analysis.

**From where data/document is obtainable**

Applicants can be communicated to correspond author be e-mail or postal address to receive the requested data. Postal address: Nutrition Department, School of Public Health, Iran University of Medical Sciences, Hemat Highway, Tehran Cell phone: +982186704743 Email: n-aryaeian@sina.tums.ac.ir

**What processes are involved for a request to access data/document**

Publishing in scientific-research journals Applicants will be given access to the obtained data from current study by sending an email to correspond author.

**Comments**