Effectiveness of Curcumin in Sarcopenia: A Systematic Review Protocol

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Abstract

Background: Sarcopenia is a multifactorial disease with a progressive decline in skeletal muscle mass, muscle strength, and physical performance. Curcumin is a nutraceutical investigated for its anti-inflammatory and antioxidant properties. It is inexpensive, accessible, and considered a safe and practical approach to help alleviate symptoms of sarcopenia and improve muscle mass and function. **Objective**: This systematic review aims to obtain more conclusive evidence on the effectiveness of curcumin among adults 40 years and above with sarcopenia in improving muscle pain, strength, performance, and muscle morphology. **Methodology**: The review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. It will focus on any interventional studies on curcumin for adults diagnosed with sarcopenia, with the following outcomes: clinically significant improvement in pain, muscle strength and performance, quality of life, and improvement in muscle morphology. Studies completed until 2024 will be included. The databases to be searched include PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL Plus (EBSCOhost), Embase, and Web of Science. The identified citations will be collated in Zotero and uploaded to Covidence© to be assessed using the eligibility criteria and systematically reviewed by two independent reviewers. The CASP Randomised Controlled Trial Checklist will be utilized to assess the quality of the included studies. **Expected Results**: The results will serve as a groundwork for future sarcopenia research among allied health specialists, particularly those in the field of physiotherapy - students, healthcare practitioners, and academicians (PROSPERO registration number: CRD42023448750)

Key Words: Sarcopenia, Curcumin, Systematic Review, Systematic Review Protocol

INTRODUCTION

Sarcopenia is a clinical syndrome first identified in 1988 by Rosenberg. It is characterized by reduced muscle mass and function and is closely related to aging.[1] Sarcopenia is a progressive and generalized skeletal muscle disorder associated with an increased risk for adverse outcomes, including falls, fractures, physical disability, and even mortality.[2] The prevalence rates range from 5 to 13% among community-dwellers aged 65 and above and increase to 20 to 25% among 80 and older.[3] The variations in the prevalence are affected by population characteristics, disease status, and the diagnostic criteria and measurement tools employed.[4]

Older adults have diminished amounts of physical activity and nutritional intake due to various biological and physiological changes associated with aging. Reduced protein and caloric intake hasten the decline of muscle mass and function. Furthermore, several mechanisms explain the core pathogenesis of sarcopenia, including chronic disease conditions, inflammatory pathway activation, and various cellular and biochemical abnormalities, such as mitochondrial dysfunction, neurodegeneration, and hormonal changes.[3] Loss of skeletal muscle mass at approximately 8 percent per decade has been observed at ages 50 to 70 years. After

which, a more significant muscle mass loss at 15 per decade occurs.[3]

Sarcopenia impacts older adults in terms of physical, mental (cognitive), emotional, social, and economic burdens. A high interest in research in this field has emerged, focusing on various treatment strategies that may delay disease progression and optimally manage its clinical presentations. Sarcopenia presents with changes in physical performance, particularly observed in daily activities such as walking. Moreover, muscle pain, which may be due to the local inflammation and anabolic process occurring in the skeletal muscle as part of the sarcopenia pathophysiology, is a usual presentation. Dysregulation of the immune system occurs in aging, resulting in increased secretion of cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1, and C-reactive protein (CRP), all of which result in the production of pain.[5]

Sarcopenia interventions supported by scientific evidence to improve outcomes are resistance exercise and optimized nutritional intake.[6] The 2018 international guideline on sarcopenia strongly recommended resistance-based training, while a conditional recommendation was given for protein and caloric intake augmentation.[7] Resistance training (RT) is usually recommended to counteract age-related muscle loss.[8] Progressive resistance training has been thoroughly investigated to improve and enhance muscle strength, size, and functional capacity in older adults.[9] However, a 2009 Cochrane review of 121 trials with 6,700 participants evaluating the effect and safety of progressive resistance strength training on older adults reported joint pain and muscle soreness as the usual musculoskeletal adverse events.[10] For any pain, pharmacological treatment is the mainstay of management. The World Health Organization formulated the pain ladder to guide clinicians in choosing pharmacological treatments. Different analgesics ranging from paracetamol to nonsteroidal anti-inflammatory drugs (NSAIDs) to centrally-acting (*i.e.*, opioid) analgesics (CAA), have been widely used in pain treatment.[11] However, there are identified risks associated with the intake of these drugs, such as cardiovascular,[12] gastrointestinal,[13] and renal[14,15] adverse effects from the use of NSAIDs, and

potential abuse and dependence on the use of CAA.[16]

In recent years, the therapeutic benefits of nutraceuticals and herbal medicines for sarcopenia management have been explored. Natural products derived from commonly available herbs and plants, referred to as nutraceuticals, have been investigated for their therapeutic benefits because of their anti-inflammatory and antioxidant properties. The rhizome *Curcuma longa linn (C. longa)* or turmeric, belongs to the Zingiberaceae (ginger) family and is a perennial plant widely grown in different Asian countries, including the Philippines. Curcumin, a polyphenol from *C. longa*, is well-known for its anti-inflammatory, antioxidant, and anti-aging benefits.[17] The use of curcumin has been demonstrated in preclinical studies to be an attainable solution for preventing and treating muscle wasting.[18] The effectiveness of nutraceutical products in improving muscle function and performance has been demonstrated in several clinical studies. Rattanaseth et al. demonstrated the benefit of curcumin in post-exercise muscle soreness among young individuals aged 19.5 to 36 years in a systematic review of thirteen randomized controlled trials.[19] The CurChexia study on patients with cancer cachexia demonstrated that adjunct curcumin (four capsules of 500 mg administered for a period of eight weeks) resulted in a significant muscle mass improvement compared to standard nutritional support alone.[20] Curcumin was approved by the U.S. Food and Drug Administration as "Generally Recognized As Safe" (GRAS), with a good safety profile and tolerability established in clinical studies.[21]

Natural products such as curcumin are less expensive, more accessible, and considered safe (*i.e.*, with low toxicity) compared to drugs and high-protein dietary approaches; thus, curcumin may be a practical approach to help alleviate muscle pain and delay sarcopenia progression. Most of the systematic reviews on curcumin were on joint pains (particularly the knee) associated with osteoarthritis[22-24] and muscle pain and soreness among healthy young adults.[19,25-27] Therefore, this systematic review aims to obtain more conclusive evidence on the effectiveness of curcumin on sarcopenia among

adults 40 years and above in terms of clinical improvement in pain, muscle performance and strength, quality of life, and improvement in morphology of skeletal muscle using diagnostic procedures. This systematic review protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines.

METHODS

The systematic review protocol has been submitted to PROSPERO, an international database of prospectively registered systematic reviews (registration number: CRD42023448750).

Eligibility Criteria

Population (P). This review will include human studies on adults 40 years and above, clinically diagnosed with sarcopenia, both community-dwelling and institutionalized (*e.g.,* hospital, medical treatment facility, nursing home, acute care facility).

Intervention (I). Studies that evaluated the use of oral turmeric, turmeric extract, curcumin, or curcuminoids as an active ingredient of finished product/s. Interventions and comparators are eligible regardless of dose/s or strengths, delivery, and duration of intake will be included in the review.

Control (C). The search will be limited to studies with the following as comparators: placebo, commonly used nutraceuticals and food supplements such as vitamins and minerals, glucosamine, and chondroitin, the usual treatment, standard of care, resistance exercise, and no treatment.

All studies that include younger adults (less than 40 years old) engaged in professional athletic activities or performance will be excluded from this review. Likewise, studies involving old-age adults with the following conditions will not be included: (1) dementia or any cognitive impairments, (2) behavioral or psychological disorders or conditions, (3) physical disabilities or any conditions affecting mobility, and (4) problems in balance and coordination. To be excluded also are studies on cachexia, frailty, myopenia, dynapenia, or muscle disorders with secondary causes such as hereditary, metabolic, or malignancy. The following interventional studies will not be included: (1) involving other complementary and alternative medicines and other management not mentioned in the inclusion criteria and (2) non-human studies. This review will not include qualitative studies, review papers, white papers, medical position papers, book chapters, correspondence, or letters from the editor/s.

Outcomes (O). Primary outcomes include significant improvement in: (1) pain (measured by visual analog scales, categorical verbal rating scales, and categorical numerical rating scales, or through pain diaries or pain questionnaires), (2) muscle strength (grip strength, chair stand/rise test), (3) muscle performance (measured by gait speed, timed up and go test or short physical performance battery), (4) quality of life (measured by SarQoL or health-related quality of life [HRQoL]), (5) muscle morphology (measured using computed tomography [CT scan], magnetic resonance imaging [MRI], dual energy X-ray absorptiometry [DXA], bioelectrical impedance analysis [BIA], or ultrasound/sonography). The secondary outcomes include safety data (reported as adverse events).

Types of studies. Any interventional studies on humans (randomized and non-randomized controlled trials) in the English language, published from inception until December 31, 2023, will be included in this systematic review.

Information Sources and Search Strategy. Using the PICO (population, intervention, control, and outcomes), literature search strategies will be developed using medical subject headings (MeSH) and text words related to curcumin, curcuminoid, turmeric, sarcopenia, age-related muscle disease, and muscle aging.

The databases to be searched will include PubMed, CINAHL Plus (EBSCOhost), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. If only the abstracts of the eligible studies are available, the author/s of the studies will be contacted to request full text/s. Unpublished clinical studies will be searched on Clinicaltrials.gov. (to include unpublished studies presented in international conferences). All identified citations will be

collated using a reference management software, Zotero.

The sample search strategy to be used for this review is presented in Tables 1 and 2.

Data Management. To facilitate effective collaboration among the reviewers, the results of the literature search will be uploaded to Covidence©, an internet-based software. Covidence© will consolidate search results from the different databases and remove duplicate records of the same study.

Selection Process. The primary author will search for studies and collate and organize all identified citations in Zotero. Utilizing PICO, the two review authors will independently screen the titles and abstracts, after which the full reports of all included studies will be obtained and reviewed. If only the abstracts of the eligible studies are available, the author(s) of the studies will be contacted to request full text. The review authors will not be blinded to the complete information of the eligible studies, including journal titles, study authors, and institutional affiliations. The reasons for the exclusion of studies will be documented. Any disagreements will be resolved by discussion between the two review authors. The third author may take part

in the discussion and help resolve any disagreements.

Data Collection Process and Data Items. A data extraction template will be generated from Covidence© to facilitate data analysis and synthesis effectively. Utilizing data extraction tables (Microsoft Excel), the principal investigator (Reviewer 1) will extract all relevant information from the selected records/studies, including the following: (1) study details such as study identifier, main author's name, publication date, sponsorship sources, and study objective/s; (2) study design; (3) population/participants (e.g., number of participants, mean age, body mass index); (4) outcomes and outcome measures; (5) types of therapeutic interventions and intervention characteristics (e.g., dosage strength, frequency of intake, length of therapy); (6) diagnostic procedures utilized; (7) efficacy and safety results (*e.g.*, muscle morphology, muscle performance and strength, adverse events).

Risk of Bias Assessment. The Critical Appraisal Skills Programme (CASP),[28] specifically the CASP Randomised Controlled Trial (RCT) Checklist, will be utilized by the two trained study reviewers to assess the quality of the included studies.

Table 1. Sample of Search Strategy (PubMed-MEDLINE)

Search Strategy	Results
(((((((((curcumin*[MeSH Terms]) OR curcuma[MeSH Terms]) OR curcuminoid[MeSH Terms])) AND (((sarcopenia[MeSH Terms]) AND sarcopenia[Abstract]) AND sarcopenia[Title])) AND (((muscle decline[MeSH Terms]) OR muscle decline[Abstract]) OR muscle decline[Title]) AND (((((age-related[MeSH Terms]) OR age-related[Abstract]) OR age-related[Title])) AND (((muscle decline[MeSH Terms]) OR muscle decline[Abstract]) OR muscle decline[Title]))) OR (((age-associated[MeSH Terms]) OR age-associated[Abstract]) OR age associated[Title])) AND (((adult* AND 40 year*[Abstract]) OR adult* AND more than 40 year*[Abstract]) OR old adult*[Abstract])) AND (((((((human study[Abstract]) OR human trial[Abstract]) OR clinical study[Abstract]) OR clinical trial)) NOT animal study[Abstract]) NOT animal trial[Abstract])	197 Date last searched: 29 Dec 2023

Table 2. Sample Search Strategy from EBSCO Host

Search Strategy	Results
Curcumin OR curcuma longa OR (turmeric or turmeric extract) AND (sarcopenia or sarcopenic) OR muscle wasting AND age-related OR age associated AND (clinical study or clinical trial) AND (adults 40 years or older)	392 Date last searched: 29 Dec 2023

The CASP-RCT checklist is a structured list of eleven (11) questions to guide in evaluating the study's validity, methodological rigor, results,

and clinical relevance. The quality of each study will be classified as high, moderate, or low. The quality assessment will be presented in tabular

form and will include the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of biases.

Data Synthesis. Descriptive statistics will be used for the demographics dataset. Continuous data will be presented as standardized mean difference (SMD) with 95% confidence intervals. If the data obtained from the studies are similar enough to estimate an average effect (*i.e.*, are statistically homogeneous), a meta-analysis will be performed using Review Manager (RevMan) [Computer program] Version 7.2.0. The inconsistency index (I^2) will be utilized to estimate the percentage of variability in the results across the different studies. A random-effects model will be used to manage the heterogeneity of studies in terms of study design, formulation used (unformulated or improved bioavailability), curcumin dose, duration of treatment, and demographic characteristics of individual studies. The results of the meta-analysis will be presented using a forest plot. If the data of all included studies are not statistically homogeneous, then a narrative synthesis will be conducted instead.

Possible meta-biases will be avoided by strict adherence to the eligibility criteria, and detailed quality (risk of bias) assessments of all included studies.

EXPECTED RESULTS

This systematic review will further identify gaps or needs, deficiencies, and trends in the current evidence, which can be helpful in future research. Likewise, it will determine a natural product's feasibility, relevance, and effectiveness for a specified disease condition, i.e., sarcopenia. The study results and findings will furnish foundational evidence for future sarcopenia research among different stakeholders, particularly in the field of physiotherapy - students, healthcare practitioners, and academicians.

Individual author's contributions

MAD is the primary author and reviewer in charge of conceptualization, methodology, title and abstract screening, full-text review, data extraction, and writing (protocol and final manuscript). JE is the second reviewer to screen the titles and abstracts and review full texts. If there is a need to resolve disagreements or discrepancies, SM will act as the third reviewer. SM and RLR reviewed the study protocol and will review the data synthesis, analyses, and final manuscript.

Disclosure statement

Conflicts of interest

SM is part of the Editorial Board of PJAHS.

Supplementary Materials

[**Supplementary Material A**](). PRISMA-P 2015 checklist

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