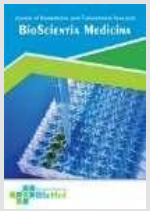
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Osteoprotective and Chondroprotective Effects of *Moringa oleifera*: A Systematic Literature Review

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ARTICLE INFO

Keywords:
Arthritis
Chondroprotective
Moringa oleifera
Osteoporosis
Osteoprotective

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i6.1316

A B S T R A C T

Background: Bone and joint disorders, particularly arthritis and osteoporosis, represent significant global health burdens, often managed with NSAIDs and steroids, which carry potential systemic side effects. *Moringa oleifera*, a plant rich in bioactive compounds, has emerged as a potential therapeutic alternative due to its reported biological activities, including anti-inflammatory and antioxidant effects. This systematic review aimed to evaluate the existing preclinical evidence regarding the osteoprotective (bone-protective) and chondroprotective (cartilage-protective) effects of *Moringa oleifera*. **Methods:** A systematic literature search was conducted following PRISMA guidelines across PubMed, Science Direct, and Google Scholar databases for relevant English-language articles published between 2014 and 2024. Studies investigating the effects of *Moringa oleifera* extracts on bone or cartilage health in in vivo arthritis or bone defect models were included. Data on study design, intervention details, outcome measures, and key findings related to osteoprotection and chondroprotection were extracted and synthesized qualitatively. **Results:** Seven preclinical *in vivo* studies met the inclusion criteria. The included studies demonstrated that various extracts of *Moringa oleifera* (leaf ethanol, aqueous, methanol) exerted significant anti-inflammatory effects, evidenced by reduced paw edema, lower arthritis scores, and decreased inflammatory markers like CRP. Anti-nociceptive effects were also observed. Chondroprotective effects were indicated by improved radiographic scores (reduced joint space narrowing), cartilage regeneration, reduced fibrillation, and preservation of chondrocytes in histopathological analyses. Osteoprotective effects included increased osteoblast numbers, improved trabecular bone microarchitecture, decreased osteoclast numbers, reduced bone resorption, and enhanced bone healing, particularly when combined with marine collagen. **Conclusion:** Preclinical evidence strongly suggested that *Moringa oleifera* possesses significant osteoprotective and chondroprotective properties, mediated likely through its anti-inflammatory, anti-nociceptive, antioxidant, and direct cellular effects on bone and cartilage cells. *Moringa oleifera* holds potential as a supplementary or alternative therapeutic strategy for managing bone and joint diseases like arthritis and osteoporosis, although further rigorous clinical investigation is warranted.

1. Introduction

Musculoskeletal disorders constitute a substantial global health challenge, with inflammatory joint diseases like arthritis and bone loss conditions such as osteoporosis being major contributors to chronic pain, disability, and diminished quality of life. Arthritis is characterized by a spectrum of conditions that lead to inflammation within the joints, resulting in pain, stiffness, and the eventual deterioration of articular cartilage and the underlying bone structure. Osteoporosis, on the other hand, is a progressive condition involving the reduction of bone mass and the deterioration of bone microarchitecture, which consequently elevates the risk of bone fragility and

fractures. The current pharmacological management of arthritis primarily relies on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. NSAIDs are effective in managing the symptoms of arthritis by inhibiting cyclooxygenase enzymes, which reduces the production of prostaglandins and thereby alleviates inflammation. Similarly, corticosteroids provide broad anti-inflammatory effects. However, the long-term use of these medications is frequently associated with significant systemic side effects, including complications related to the gastrointestinal, cardiovascular, renal, and metabolic systems, which can limit their use and negatively impact patient adherence to treatment regimens.[1-3]

Likewise, while treatments for osteoporosis can be effective, they may also present with adverse effects and might not fully restore the structural integrity of bone. These limitations have catalyzed a surge of interest in exploring alternative and complementary therapeutic approaches, with a focus on natural sources such as medicinal plants. Herbal remedies have a long-standing history in traditional medicine systems, where they have been utilized for centuries in the management of various ailments, including musculoskeletal conditions. Contemporary research endeavors are now directed towards providing scientific validation for these traditional applications and identifying the specific bioactive compounds responsible for their therapeutic effects. *Moringa oleifera* Lam. (family Moringaceae), commonly known as the drumstick tree, is a plant indigenous to the Indian subcontinent that is now widely cultivated in tropical and subtropical regions across the globe. This plant has garnered recognition as a "miracle tree" due to its rich nutritional composition and the diverse array of medicinal properties attributed to it. Various parts of the *Moringa oleifera* plant, including the leaves, seeds, pods, roots, and flowers, are abundant sources of essential nutrients such as vitamins, minerals, and proteins, as well as a wide variety of bioactive phytochemicals. These phytochemicals include phenolic compounds like flavonoids (such as quercetin and kaempferol), alkaloids (such as moringine), carotenoids, tannins, and saponins. It is believed that these compounds are instrumental in contributing to the plant's diverse range of pharmacological activities, which encompass antioxidant, anti-inflammatory, anti-diabetic, hepatoprotective, cardioprotective, and anti-cancer effects.[4-7]

Given its potent anti-inflammatory and antioxidant properties, *Moringa oleifera* has been the subject of investigation for its potential therapeutic benefits in managing inflammatory conditions such as arthritis. Furthermore, emerging evidence indicates that *Moringa oleifera* may also play a role in promoting bone health and protecting cartilage. Osteoprotective effects refer to the capacity of a substance to protect bone cells, maintain bone mass and structure, and facilitate bone formation or healing. Chondroprotective effects, conversely, pertain to the ability to protect chondrocytes (the cells of cartilage), preserve the integrity of the cartilage matrix, and mitigate cartilage degradation. Despite the growing interest in *Moringa oleifera* and its potential therapeutic applications, there is a lack of a comprehensive synthesis of evidence that specifically examines its dual protective effects on both bone and cartilage tissues. To address this gap in the existing literature, this systematic review was conducted.[8-10] This review aims to critically evaluate and summarize the available preclinical evidence derived from *in vivo* studies concerning the osteoprotective and chondroprotective effects of *Moringa oleifera* extracts.

2. Methods

This systematic review was conducted in adherence to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The PRISMA guidelines are designed to ensure transparency and completeness in the reporting of systematic reviews, thereby enhancing the reliability and validity of the findings.

The studies included in this review were required to fulfill a set of predefined eligibility criteria. These

criteria were established to ensure that the selected studies were relevant to the research question and of sufficient quality to contribute meaningful data to the synthesis. Firstly, studies were considered eligible if they investigated the effects of any extract derived from *Moringa oleifera*. This criterion ensured that the review encompassed the full range of potential applications of the plant, irrespective of the specific part used (e.g., leaves, seeds, roots) or the extraction method employed. Secondly, only studies that utilized in vivo animal models relevant to bone or joint disease were included. This criterion focused the review on preclinical studies that directly assessed the effects of *Moringa oleifera* in living organisms, specifically in the context of conditions affecting bone and joint health. Examples of relevant animal models include those with induced arthritis, osteoporosis, or bone defects. Thirdly, studies were required to have assessed outcomes related to either bone health (osteoprotection) or joint cartilage health (chondroprotection), or both. This criterion ensured that the review specifically addressed the osteoprotective and chondroprotective effects of *Moringa oleifera*, which was the primary focus of the research question. Osteoprotection was defined to include measures such as bone mineral density, bone microarchitecture, osteoblast and osteoclast activity, bone formation markers, and bone healing. Chondroprotection was defined to include measures such as arthritis scores, joint swelling, cartilage histology, chondrocyte viability, levels of inflammatory markers in joint tissue, and radiographic joint changes. Fourthly, studies were required to include a control group. The inclusion of a control group (e.g., placebo, vehicle, no treatment, or standard treatment such as NSAIDs or estradiol) was essential for establishing a basis for comparison and determining the specific effects of *Moringa oleifera* treatment. Fifthly, studies were required to be published in the English language. This language restriction was applied due to resource constraints and the need for the reviewers to be able to accurately and efficiently assess the studies. Sixthly, studies were required to be published between January 2014 and December 2024. This criterion was established to focus the review on the most recent evidence available, reflecting current research practices and knowledge in the field. Seventhly, studies were required to be full-text original research articles. This criterion excluded reviews, abstracts, proceedings, letters, and conference papers, ensuring that the review was based on primary research data.

A comprehensive literature search was conducted across major electronic databases to identify relevant studies. The databases searched were PubMed, Science Direct, and Google Scholar. These databases were chosen because they are widely recognized as comprehensive sources of biomedical and scientific literature. The search strategy employed a combination of Medical Subject Headings (MeSH terms), where applicable, and keywords. MeSH terms are a controlled vocabulary used for indexing articles in PubMed, which helps to ensure consistency and accuracy in the search process. Keywords were used to supplement the MeSH terms and capture a broader range of relevant articles. Boolean operators (AND, OR) were used to combine the search terms and refine the search results. The use of Boolean operators allowed for a more precise search strategy, ensuring that only articles that met the specific criteria were retrieved. The key search terms used included: ("Moringa oleifera" OR "Moringa") AND ("arthritis" OR "osteoarthritis" OR "rheumatoid arthritis" OR "antiarthritic" OR "anti-arthritis" OR "joint" OR "cartilage" OR "chondroprotective") OR ("bone" OR "osteoporosis" OR "osteoblast" OR "osteoclast" OR "bone density" OR "osteoprotective" OR "bone healing"). These search terms were carefully chosen to capture the relevant concepts of the intervention (*Moringa oleifera*) and the outcomes of interest (bone and joint health). The terms were combined using Boolean operators to ensure that the search retrieved articles that addressed both the intervention and the outcomes. The search was restricted to articles published between 2014 and early 2025 and written in the English language. These restrictions were

applied to ensure that the review focused on recent, English-language studies, as specified in the eligibility criteria. In addition to the electronic database searches, the reference lists of identified relevant reviews and included studies were manually screened for any additional potentially eligible articles. This manual screening helped to identify articles that may not have been captured by the database searches, ensuring a more comprehensive search.

The search results from the electronic databases were imported into reference management software. Reference management software is used to organize and manage bibliographic data, which facilitates the screening and selection process. Duplicates were then removed to ensure that each article was only screened once. Two reviewers independently screened the titles and abstracts of the retrieved articles based on the predefined eligibility criteria. This independent screening process helped to reduce bias and ensure consistency in the selection of articles. The title and abstract screening allowed for a quick initial assessment of the relevance of each article. Full texts of potentially relevant articles were then obtained and assessed independently by the two reviewers for final inclusion in the review. This full-text assessment involved a more detailed evaluation of the articles to determine whether they met all of the eligibility criteria. Any disagreements that arose during the screening or eligibility assessment phases were resolved through discussion and consensus between the two reviewers. If necessary, a third reviewer was consulted to help resolve any persistent disagreements. This process ensured that the final selection of articles was based on a consensus view. The reasons for excluding articles at the full-text stage were carefully documented. This documentation provides transparency and allows readers to understand the rationale behind the inclusion and exclusion of specific studies. The entire article selection process was documented using a PRISMA flow diagram. A PRISMA flow diagram provides a visual representation of the study selection process, including the number of articles identified, screened, and included or excluded at each stage. This diagram helps to enhance the transparency and clarity of the review process.

A standardized data extraction form was developed and used by two independent reviewers to extract relevant information from each included study. The use of a standardized form ensured that the data extraction process was consistent and comprehensive. The independent extraction by two reviewers helped to minimize errors and bias. The data extracted from each study included; First author and publication year. This information is important for identifying the studies and tracking their citations; Study design and animal model characteristics. This included details such as the species, strain, and sex of the animals used, as well as the method used to induce the bone or joint disease. These details are important for assessing the generalizability of the findings and identifying potential sources of heterogeneity; Intervention details. This included information on the specific part of the *Moringa oleifera* plant used, the extraction method employed, and the dose, route, and duration of administration of the extract. These details are crucial for understanding the specific treatment being evaluated and for comparing the results across studies; Control group details. This included information on the type of control group used (e.g., placebo, vehicle, no treatment, or standard treatment) and any specific treatments administered to the control group; Key outcome measures related to osteoprotection and chondroprotection. This included the specific parameters measured and the methods used to measure them. For osteoprotection, examples of parameters include bone mineral density, bone microarchitecture parameters (e.g., BV/TV, Tb.Th, Tb.N, Ct.Th), osteoblast and osteoclast activity, and bone formation markers. For chondroprotection, examples include arthritis scores, joint swelling, cartilage histology (e.g., using scoring systems like OARSI), chondrocyte viability, levels of inflammatory markers in joint tissue (e.g., CRP), and radiographic joint changes; Main findings and reported statistical significance. This included the key results of the study

and the statistical significance of those results (e.g., p-values). Any discrepancies that arose during the data extraction process were resolved by consensus between the two reviewers. If necessary, a third-party adjudication was used to resolve any persistent disagreements. This process ensured the accuracy and consistency of the extracted data.

Due to the expected heterogeneity in animal models, *Moringa oleifera* extracts, dosages, and outcome measures across the included studies, a meta-analysis was not planned. Meta-analysis is a statistical technique that combines the results of multiple studies to provide a pooled estimate of the effect of an intervention. However, it is only appropriate when the studies being combined are sufficiently similar in terms of their design and methodology. In this case, the anticipated heterogeneity made a narrative synthesis of the findings more appropriate. Instead of a meta-analysis, the findings of the included studies were synthesized narratively. Narrative synthesis is a method of summarizing and explaining the findings of multiple studies using a descriptive and interpretive approach. It allows for the synthesis of evidence from studies with diverse designs and methodologies. The results were grouped based on the primary focus of the studies: chondroprotective effects (including anti-inflammatory and anti-nociceptive actions relevant to joints) and osteoprotective effects. This grouping helped to organize the findings and facilitate a clear presentation of the evidence. Key findings for each outcome measure were described and compared across studies. This involved identifying patterns and trends in the results, as well as noting any inconsistencies or differences between studies. Particular attention was paid to dose-response relationships, where reported, to assess whether the effect of *Moringa oleifera* varied with the dose administered. A summary table was created to present the characteristics and key findings of each included study. This table provided a concise overview of the studies, including details such as the study design, animal model, intervention, and main results. It facilitated comparison across studies and helped to highlight the main findings of the review.

A quality assessment of the included studies was planned using a recognized tool. The quality assessment is a critical step in a systematic review, as it allows for an evaluation of the methodological rigor and potential bias of the included studies. This assessment helps to determine the reliability and validity of the findings of the review. Specifically, SYRCLE's risk of bias tool for animal studies was intended to be used. SYRCLE's tool is a widely used and validated tool for assessing the risk of bias in preclinical animal studies. It assesses various domains of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain is assessed as having a low, high, or unclear risk of bias. The results of the quality assessment were intended to be used to inform the interpretation of the findings of the review. Studies with a high risk of bias may be given less weight in the synthesis of the evidence, while studies with a low risk of bias may be given more weight.

3. Results

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The process began with the identification of 1443 records through database searching. This represents the total number of initial records retrieved from the electronic databases using the defined search strategy; Screening: Following the identification stage, 3 records were removed due to being duplicates, resulting in 1440 records proceeding to the screening phase. During the screening of titles and abstracts, 1298 records were excluded. The reasons for exclusion included being identified by automated tools, being reviews, or being deemed irrelevant to the topic of the review; Included: After the screening and eligibility assessment processes, 7 studies met all the inclusion criteria and were included in the qualitative synthesis. These 7 studies represent the final set of evidence used to address the research question of the systematic review.

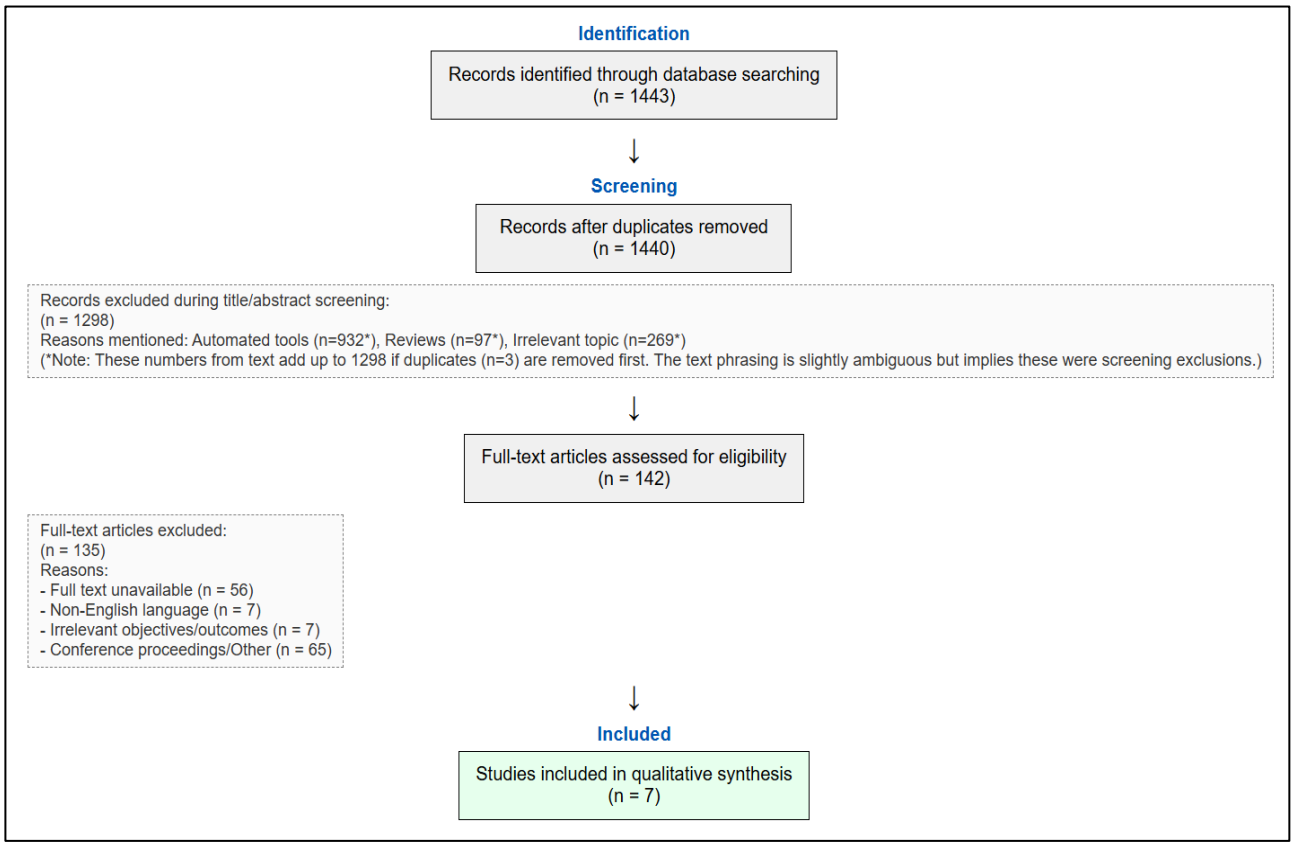

Figure 1. PRISMA flow diagram.

Table 1 presents a summary of the seven preclinical studies included in the systematic review. It outlines the key characteristics of each study, including the animal model used, the *Moringa oleifera* intervention administered, the comparator groups, and the main findings related to chondroprotective and osteoprotective effects; Animal Models and Conditions: The studies utilized a variety of animal models to investigate the effects of *Moringa oleifera*. The majority of studies (5 out of 7) employed rat models of arthritis, induced by different methods such as formalin or Complete Freund's Adjuvant (CFA). These models aimed to mimic the inflammatory processes observed in human arthritis. One study used mice to assess bone healing in a defect model, and another used ovariectomized rats to model post-menopausal osteoporosis. This diversity in models allows for an assessment of *Moringa oleifera*'s effects across different contexts of bone and joint disease; Moringa oleifera Interventions: The interventions involved different extracts of *Moringa oleifera*, primarily administered orally. Aqueous and ethanol extracts were most common, but methanol and ethyl acetate extracts were also used in one study. Dosages varied, ranging from 250 mg/kg body weight to 4g/100g body weight. One study used local application of the extract. This variation in extract type and dosage highlights the need to consider the potential influence of preparation methods and concentrations on the observed effects; Comparator Groups: The comparator groups varied across studies. Most studies included a negative control (untreated arthritis or bone defect model) and a positive control using a standard anti-inflammatory drug (e.g., Diclofenac sodium, Indomethacin, Piroxicam) or another treatment (Vitamin D, Estradiol valerate, Marine Collagen). These comparators provide a basis for evaluating the efficacy of *Moringa oleifera* relative to existing treatments or the natural progression of the disease. The table summarizes findings related to

chondroprotection (often including anti-inflammatory and anti-nociceptive effects) and osteoprotection; Chondroprotection/Anti-inflammatory: Several studies reported significant anti-inflammatory effects of *Moringa oleifera* extracts, as evidenced by reduced paw edema, decreased arthritis scores, and decreased levels of inflammatory markers like CRP. Histopathological analyses indicated potential chondroprotective effects, including cartilage regeneration and reduced cartilage damage, although some studies also reported dose-dependent effects with cartilage thinning or erosion at lower or higher doses; Anti-nociceptive effects were observed in one study, suggesting that *Moringa oleifera* can also alleviate pain associated with arthritis; Osteoprotection: Two studies specifically examined osteoprotective effects. One found that *Moringa oleifera* enhanced bone healing in a bone defect model, increasing osteoblast count and improving bone formation. The other study in ovariectomized rats showed that *Moringa oleifera* improved bone microarchitecture, increased bone formation markers, and decreased bone resorption.

Table 2 presents a focused summary of the effects of *Moringa oleifera* on inflammation, pain, and cartilage health in the included animal studies. It organizes the findings by study, highlighting the specific model and intervention used, and then detailing the observed anti-inflammatory, anti-nociceptive, and chondroprotective effects; Anti-inflammatory Findings: Several studies demonstrated significant anti-inflammatory effects of *Moringa oleifera*. This was consistently observed as a reduction in paw edema, a common measure of inflammation in arthritis models. One study (Fatima et al., 2021) also reported a significant decrease in serum CRP levels, a systemic marker of inflammation. Saleem et al. (2020) provided evidence of both in vitro and in vivo anti-inflammatory activity, including antioxidant effects, inhibition of protein denaturation, prevention of red blood cell membrane lysis, and anti-proteinase activity. The *in vivo* results showed substantial edema inhibition, with one *Moringa oleifera* extract demonstrating greater efficacy than the standard anti-inflammatory drug Piroxicam. Mahdi et al. (2018) also found significant inhibition of paw edema and a reduction in arthritis index scores, indicating an overall decrease in arthritis-related inflammation; Anti-nociceptive Findings: Anti-nociceptive effects, indicating pain relief, were specifically assessed in one study (Mahdi et al., 2018). This study reported significant dose-dependent anti-nociceptive activity of *Moringa oleifera*. The effects of *Moringa oleifera* on pain relief were observed to occur earlier than those of the standard drug, Indomethacin. Other studies, while not explicitly measuring anti-nociception, suggest that the observed reduction in arthritis scores may indirectly reflect some degree of pain relief, as pain is a major contributor to these scores; Chondroprotective Findings: Chondroprotective effects, indicating protection of cartilage, were primarily assessed through histological examination of cartilage tissue. Fatima et al. (2021) reported dose-dependent histological findings, with higher doses of aqueous extract showing evidence of cartilage regeneration and new bone formation. Shahid et al. (2024) used the OARSI scoring system to quantify cartilage damage. *Moringa oleifera* treatment significantly reduced cartilage damage compared to the control group. Saleem et al. (2020) also observed dose-dependent effects on cartilage histology, with higher doses of *Moringa oleifera* extracts showing minimal inflammation and no cartilage erosion. Mahdi et al. (2018) assessed chondroprotection using radiography, showing a significant reduction in joint space narrowing, a hallmark of cartilage degradation in arthritis. Another study by Shahid et al. (2024) demonstrated that *Moringa oleifera* delayed cartilage damage compared to controls and was more effective than Vitamin D in repairing joint cartilage damage.

Table 1. Characteristics and key findings of included studies on *Moringa oleifera* (MO).

Author(s) & year	Animal model & condition	*Moringa oleifera* intervention	Comparator(s)	Key findings (Chondroprotective & Osteoprotective)
Fatima, et al. (2021)	Wistar rat arthritis model (Formalin-induced)	• MO ethanol extract (250 & 500 mg/kg bw); • MO aqueous extract (500 mg/kg bw)	• Normal mice; • Rat arthritis model (untreated); • Rat arthritis model + Diclofenac sodium (10 mg/kg bw)	• Chondroprotective/Anti-inflammatory: Significant reduction in paw edema, thickness, and arthritis scores with MO extracts (aqueous extract most potent); Significant decrease in CRP levels; • Histopathology (Cartilage/Bone): Dose-dependent effects: Cartilage thinning/bone erosion (ethanol 250); Hypertrophic tissue/erosion (ethanol 500); Cartilage regeneration & new bone formation with mild synovial changes (aqueous 500).
Shahid, et al. (2024)	Sprague Dawley male rat model of arthritis	• MO aqueous extract (500 mg/kg bw)	• Control mice; • Negative control mice; • Rat arthritis model + Vitamin D (4000 IU/kg bw)	• Chondroprotective (Histopathology - OARSI score): MO group showed significantly less cartilage damage vs Vitamin D group ($p<0.01$); 70% MO rats had only surface fibrillation (OARSI I), 30% had deep fibrillation limited to superficial zone (OARSI II); Vitamin D group showed more severe damage (OARSI I, II, and III).
Saleem, et al. (2020)	Wistar rat arthritis model	• MO methanol extract (150, 300, 600 mg/kg bw); • MO aqueous extract (150, 300, 600 mg/kg bw); • MO ethyl acetate extract (150, 300, 600 mg/kg bw)	• Normal mice; • Rat arthritis model (untreated); • Rat arthritis model + Piroxicam (10 mg/kg bw)	• Antioxidant/Anti-inflammatory: All extracts showed antioxidant and in vitro anti-inflammatory effects (protein denaturation, membrane lysis, anti-proteinase); Methanol extract (600 mg/kg) showed maximal edema inhibition (82.28%), higher than Piroxicam; • Chondroprotective (Histopathology): Dose-dependent effect; Severe inflammation/erosion at 150/300 mg/kg (methanol/aqueous); Minimal inflammation, no pannus/erosion at 600 mg/kg; Ethyl acetate showed minimal improvement.
Mahdi, et al. (2018)	Rat arthritis model (CFA-induced)	• MO ethanol extract (250 & 500 mg/kg bw)	• Normal mice; • Rat arthritis model (untreated); • Rat arthritis model + Indomethacin (2.5 mg/kg bw)	• Anti-inflammatory/Anti-nociceptive: Significant inhibition of paw edema (250 mg/kg more active than Indomethacin); Significant reduction in arthritis index (250 mg/kg better than 500 mg/kg or Indomethacin); Significant dose-dependent anti-nociceptive activity (500 mg/kg peak at day 21, earlier than Indomethacin).; • Chondroprotective (Radiography): Significant reduction in joint space narrowing score vs controls ($p<0.001$).
Shahid, et al. (2024)	Sprague Dawley male rat model of arthritis	• MO aqueous extract (500 mg/kg bw)	• Control mice; • Negative control mice; • Rat arthritis model + Vitamin D (4000 IU/kg bw)	• Chondroprotective (Histopathology): Both MO and Vitamin D significantly delayed cartilage damage (reduced depth) vs controls ($p<0.01$, $p<0.09$ respectively); MO extract was significantly more effective than Vitamin D in repairing joint cartilage damage ($p<0.01$).
Areej, et al. (2021)	Albino mouse model of intraosseous defect (Bone healing)	• MO ethanol extract (local application)	• Control mice (defect only); • Rat model + Marine Collagen; • Rat model + MO + Marine Collagen	• Osteoprotective (Bone Healing): Significant increase in osteoblast count in MO group vs control at 2 weeks ($p=0.005$); Histology showed mature bone formation at 4 weeks; Combination MO + Marine Collagen showed most regular osteoid, thickest trabeculae, and highest increase in osteocytes & osteoblasts at 4 weeks.
Hu, et al. (2023)	Female Sprague Dawley rat model (Post-menopausal Osteoporosis - OVX)	• MO extract powder (4g/100g bw/day)	• Control rats (Sham OVX); • Rat model (OVX untreated); • Rat model + Estradiol valerate (0.1 mg/kg bw/day)	• Osteoprotective (Micro-CT & Histo): MO significantly improved trabecular microarchitecture (↑ BV/TV, Tb.Th, Tb.N, Conn.D; ↓ Tb.Sp, SMI) vs OVX model ($p<0.05$); Improved cortical parameters; Histopathology showed improved trabecular structure, comparable to control; Lower number of osteoclasts vs OVX model; MO reduced bone resorption by inhibiting abnormal osteoclast activity.

Table 2. Summary of chondroprotective, anti-inflammatory, and anti-nociceptive effects of *Moringa oleifera* (MO) from included studies.

Study (Author & Year)	Model & intervention	Anti-inflammatory findings	Anti-nociceptive findings	Chondroprotective findings (Cartilage Histology/Radiology)
Fatima, et al. (2021)	Formalin-arthritis rats; MO Ethanol (250, 500 mg/kg); MO Aqueous (500 mg/kg)	• Significant ↓ in paw edema, thickness, arthritis scores (Aqueous 500 mg/kg most potent); • Significant ↓ in serum CRP	• Not specifically assessed, but likely contributed to reduced arthritis scores.	• Histology (dose-dependent): Cartilage thinning/erosion (Ethanol 250); Hypertrophic tissue/erosion (Ethanol 500); Cartilage regeneration & new bone formation, mild synovial changes (Aqueous 500).
Shahid, et al. (2024)	Arthritis rats; MO Aqueous (500 mg/kg) vs Vit D	• Not the primary focus compared to histology, but implied by improved cartilage status.	• Not assessed.	• Histology (OARSI): MO significantly reduced cartilage damage vs Vit D ($p<0.01$); 70% MO rats = OARSI I (surface fibrillation); 30% MO rats = OARSI II (superficial zone deep fibrillation).
Saleem, et al. (2020)	Arthritis rats; MO Methanol, Aqueous, Ethyl Acetate (150, 300, 600 mg/kg each)	• In vitro: Antioxidant; ↓ protein denaturation; prevent RBC membrane lysis; anti-proteinase activity; • In vivo: Max edema inhibition (82.28%) with Methanol 600 mg/kg (higher than Piroxicam).	• Not specifically assessed.	• Histology (dose-dependent): Severe inflammation/erosion (150/300 mg/kg, Methanol/Aqueous); Minimal inflammation, no pannus/erosion (600 mg/kg, Methanol/Aqueous); Ethyl acetate showed minimal improvement.
Mahdi, et al. (2018)	CFA-arthritis rats; MO Ethanol (250, 500 mg/kg) vs Indomethacin	• Significant inhibition of paw edema (250 mg/kg showed 70.80% inhibition, > Indomethacin 70.48%); • Significant ↓ in arthritis index (250 mg/kg better than 500 mg/kg or Indomethacin).	• Significant, dose-dependent activity (250, 500, 750 mg/kg vs control, $p<0.05/0.001$); • 500 mg/kg showed effect earlier than Indomethacin, peak at day 21.	• Radiology: Significant ↓ in joint space narrowing score (mean 3.34 for 250 mg/kg; 3.84 for 500 mg/kg vs control, $p<0.001$).
Shahid, et al. (2024)	Arthritis rats; MO Aqueous (500 mg/kg) vs Vit D	• Primarily assessed via effect on cartilage degradation.	• Not assessed.	• Histology: MO significantly delayed cartilage damage (reduced depth) vs control ($p<0.01$); MO more effective than Vitamin D ($p<0.01$).
Areej, et al. (2021)	Bone defect model; MO Ethanol (local)	• Not assessed (focus on bone healing).	• Not assessed.	• Not assessed (focus on bone healing).
Hu, et al. (2023)	OVX osteoporosis model; MO Powder (4g/100g bw)	• Not assessed (focus on bone).	• Not assessed.	• Not assessed (focus on bone).

Table 3 focuses specifically on the effects of *Moringa oleifera* on bone health in the included animal studies. It presents the animal model and condition, the *Moringa oleifera* intervention used, and the key findings related to osteoprotection, categorized as cellular effects, microarchitecture, and bone healing/resorption; Animal Models and Conditions: The studies used diverse animal models to assess osteoprotective effects. Fatima et al. (2021) used a rat model of formalin-induced arthritis, while Areej et al. (2021) used a mouse model of bone healing (intraosseous defect). Hu et al. (2023) employed an ovariectomized rat model to mimic post-menopausal osteoporosis. This variety allows for the evaluation of *Moringa oleifera*'s effects in different bone-related conditions; Moringa oleifera Interventions: *Moringa oleifera* was administered as an aqueous extract in the arthritis model and as an ethanol extract in the bone

healing model. In the osteoporosis model, it was given as a powder. Dosages and routes of administration varied, with oral administration being common and one study using local application. In one bone healing study, *Moringa oleifera* was also combined with marine collagen; Bone Formation/Healing: Fatima et al. (2021) noted "new bone formation" alongside cartilage regeneration, suggesting a potential positive effect on bone in the context of arthritis. Areej et al. (2021) provided more detailed findings in the bone defect model. They observed an increase in osteoblast count (cells responsible for bone formation) and improved bone healing, with the combination of *Moringa oleifera* and marine collagen showing the most pronounced effect on osteocyte and osteoblast activity and organization of bone tissue; Cellular Effects: Areej et al. (2021) demonstrated a direct effect of *Moringa oleifera* on bone cells by showing an increase in osteoblast count. Hu et al. (2023) found a lower number of osteoclasts (cells responsible for bone resorption) in the *Moringa oleifera*-treated group, indicating a potential to reduce bone breakdown; Bone Microarchitecture: Hu et al. (2023) used micro-CT analysis, a sophisticated technique for assessing bone structure, and found that *Moringa oleifera* significantly improved trabecular bone parameters (e.g., increased bone volume/total volume, trabecular thickness, trabecular number) and cortical bone parameters in the osteoporosis model. These improvements suggest that *Moringa oleifera* can help maintain bone strength and density; Bone Resorption: Hu et al. (2023) also showed that *Moringa oleifera* reduced bone resorption, a key factor in osteoporosis, by inhibiting abnormal osteoclast activity.

Table 3. Summary of osteoprotective effects of *Moringa oleifera* (MO).

Author(s) & year	**Animal model & condition**	***Moringa oleifera* intervention**	**Key osteoprotective findings (Cellular, Microarchitecture, Healing/Resorption)**
Fatima, et al. (2021)	Wistar rat arthritis model (Formalin-induced)	MO aqueous extract (500 mg/kg bw)	• Bone Formation (Histopathology): Mentioned "new bone formation" alongside cartilage regeneration in the MO aqueous extract group.
Areej, et al. (2021)	Albino mouse model of intraosseous defect (Bone healing)	MO ethanol extract (local application); also MO + Marine Collagen	• Cellular Effects: Significant increase in osteoblast count vs control at 2 weeks (P=0.005); MO + Marine Collagen showed the highest increase in osteocytes and osteoblasts vs all groups at 4 weeks. ; • Bone Healing/Formation (Histopathology): MO group showed irregular trabecular bone at 2 weeks, progressing to regular mature bone with osteons at 4 weeks; MO + Marine Collagen group showed more regularly arranged osteoid tissue with embedded osteocytes and thicker, more organized bone trabeculae at 4 weeks.
Hu, et al. (2023)	Female Sprague Dawley rat model (Post-menopausal Osteoporosis - OVX)	MO extract powder (4g/100g bw/day)	• Cellular Effects: Lower number of osteoclasts observed after MO intervention compared to OVX model. ; • Bone Microarchitecture (Micro-CT): Significantly improved trabecular parameters vs OVX model ($p<0.05$): Increased BV/TV, Tb.Th, Tb.N, Conn.D; Decreased Tb.Sp, SMI; Improved cortical parameters (decreased Ct.Th, Ct.Ar, PsPm; increased Tt.Ar, Ct.Po, Ma.Ar, Ec.Pm). ; • Bone Structure (Histopathology): Improvement of trabecular bone structure compared to OVX model, appeared comparable to control group. ; • Bone Resorption: MO extract reduced bone resorption and improved histopathological changes by inhibiting abnormal osteoclast activity.

µCT: Micro-Computed Tomography; BV/TV: Bone Volume/Total Volume; bw: Body Weight; Conn.D: Connectivity Density; Ct.Ar: Cortical Area; Ct.Po: Cortical Porosity; Ct.Th: Cortical Thickness; Ec.Pm: Endocortical Perimeter; Histo: Histopathology / Histological; kg: Kilogram; Ma.Ar: Marrow Area; mg: Milligram; MO: *Moringa oleifera*; OVX: Ovariectomized; PsPm: Periosteal Perimeter; SMI: Structure Model Index; Tb.N: Trabecular Number; Tb.Sp: Trabecular Separation; Tb.Th: Trabecular Thickness; Tt.Ar: Total Area.

4. Discussion

The review revealed consistent evidence that *Moringa oleifera* administration can effectively alleviate inflammation and pain associated with arthritis, while also demonstrating a capacity to protect joint cartilage from degradation. This chondroprotective effect appears to be closely intertwined with *Moringa's* potent anti-inflammatory and anti-nociceptive activities, a finding that was consistently observed across the diverse range of arthritis models employed in the included studies. The studies documented notable reductions in paw edema, a hallmark of joint inflammation, as well as decreases in overall arthritis scores following *Moringa oleifera* treatment. Furthermore, several studies measured and reported a decrease in the levels of key inflammatory markers, such as CRP, providing further evidence for the plant's ability to modulate the inflammatory response. These observed anti-inflammatory effects suggest that *Moringa oleifera* extracts can interfere with the intricate signaling pathways that drive inflammation within the joints. Phytochemical analyses of *Moringa oleifera* have identified a rich array of bioactive compounds, including flavonoids like quercetin and kaempferol, alkaloids, and saponins. It is well-established that these compounds possess notable anti-inflammatory properties and can act as modulators of the inflammatory process. For instance, quercetin, a prominent flavonoid found in *Moringa oleifera*, has been shown to inhibit the activation of NF-κB, a crucial transcription factor that plays a central role in regulating the expression of numerous pro-inflammatory genes. By suppressing NF-κB activation, quercetin can effectively dampen the production of inflammatory mediators, thereby reducing inflammation. Similarly, saponins and alkaloids, other bioactive constituents of *Moringa oleifera*, have demonstrated the ability to reduce articular swelling and modulate the production of pro-inflammatory cytokines, such as IL-1β and TNF-α, which are key players in the pathogenesis of arthritis. In addition to these mechanisms, *Moringa oleifera* extracts may exert their anti-inflammatory effects by interfering with other pathways involved in the inflammatory cascade. This includes the inhibition of enzymes such as 5-lipoxygenase and COX-2, which are responsible for the production of leukotrienes and prostaglandins, respectively, both of which contribute to inflammation and pain. Furthermore, *Moringa oleifera* has been shown to reduce the production of nitric oxide (NO) by macrophages, another important mediator of inflammation. The collective impact of these multifaceted anti-inflammatory actions likely contributes significantly to the chondroprotective effects observed in the included studies. By mitigating inflammation and reducing the levels of inflammatory mediators within the joint environment, *Moringa oleifera* creates a more favorable milieu for the preservation of cartilage integrity. This is supported by the improved histological and radiographic scores observed in the studies, which indicate a reduction in cartilage damage and an overall improvement in joint health following *Moringa oleifera* treatment.[11-14]

An important observation across several included studies was the dose-dependent nature of *Moringa oleifera's* effects. This highlights the critical role of dosage in determining the therapeutic efficacy of *Moringa oleifera* extracts. While lower doses generally demonstrated some degree of beneficial effect, higher doses often resulted in more pronounced anti-inflammatory and chondroprotective actions. However, it is crucial to note that one study (Mahdi et al., 2018) reported a potentially lower efficacy at very high doses, suggesting that there may be an optimal therapeutic window for *Moringa oleifera*. The observation of reduced activity at very high doses warrants further investigation to elucidate the underlying mechanisms. Several potential explanations can be considered. One possibility is that saturation effects may occur at higher doses, where the target receptors or enzymes become fully occupied, and increasing the dose beyond this point does not lead to any additional therapeutic benefit. Another consideration is the potential presence of anti-nutritional factors within *Moringa oleifera* extracts,

which could interfere with the absorption or bioavailability of the active compounds at very high concentrations. It is also conceivable that high doses may trigger counter-regulatory mechanisms within the body, which could attenuate the overall therapeutic response. These findings underscore the importance of carefully optimizing the dosage of *Moringa oleifera* extracts to maximize their therapeutic potential while minimizing any potential adverse effects. Further studies are needed to determine the precise dose-response relationship and identify the optimal dosage range for different therapeutic applications.[15-17]

Beyond its well-established anti-inflammatory role in joint health, this review also highlighted the direct osteoprotective actions of *Moringa oleifera*. The included studies provided compelling evidence that *Moringa oleifera* extracts can exert beneficial effects on bone cells and bone tissue. Specifically, *Moringa oleifera* extracts demonstrated the ability to stimulate the activity and proliferation of osteoblasts, the cells responsible for bone formation, while simultaneously inhibiting the activity and number of osteoclasts, the cells involved in bone resorption. This dual action ultimately leads to a reduction in bone resorption and a net increase in bone formation, contributing to the maintenance of bone mass and strength. Furthermore, several studies reported that *Moringa oleifera* treatment resulted in significant improvements in bone microarchitecture, particularly in models of osteoporosis. Micro-CT analysis revealed increases in parameters such as bone volume/total volume (BV/TV), trabecular thickness (Tb.Th), and trabecular number (Tb.N), all of which are indicators of improved bone strength and density. Additionally, *Moringa oleifera* extracts were shown to enhance bone healing in bone defect models, suggesting a potential role in promoting bone repair following injury or surgery.[18-20]

5. Conclusion

This systematic review synthesized evidence from seven preclinical in vivo studies and revealed that Moringa oleifera possesses both chondroprotective and osteoprotective effects. The chondroprotective effects are mediated through the plant's anti-inflammatory and anti-nociceptive activities, as evidenced by reduced paw edema, decreased arthritis scores, and reduced levels of inflammatory markers. The review also highlighted the osteoprotective potential of *Moringa oleifera*, with studies demonstrating its ability to enhance bone formation by stimulating osteoblast activity and proliferation while simultaneously inhibiting bone resorption by reducing osteoclast activity. Furthermore, Moringa oleifera treatment led to significant improvements in bone microarchitecture and enhanced bone healing in animal models. The findings from this review suggest that Moringa oleifera holds promise as a potential therapeutic strategy for managing bone and joint disorders, including arthritis and osteoporosis. However, it is important to acknowledge the limitations of the current evidence, which is based solely on preclinical studies. Further well-designed clinical trials are necessary to confirm these findings in humans and to determine the optimal dosage, safety, and long-term efficacy of Moringa oleifera for bone and joint health.

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