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REVIEW ARTICLE

Exploring the Safety and Therapeutic Potential of the *Moringa* Species for Musculoskeletal Disorders: A Systematic Review

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ABSTRAK

Gangguan muskuloskeletal (MSD) merupakan masalah kesihatan awam yang utama kerana menjejaskan pergerakan, produktiviti dan kualiti hidup. Minat terhadap makanan berfungsi dan nutraseutikal semakin meningkat dan spesies Moringa, yang digunakan secara meluas sebagai makanan dan kaya dengan sebatian bioaktif, kini diterokai bagi peranannya dalam kesihatan muskuloskeletal. Walau bagaimanapun, keberkesanannya dalam pengurusan MSD masih belum jelas. Ulasan sistematik ini menilai keselamatan dan potensi terapeutik Moringa dalam pengurusan MSD berdasarkan garis panduan "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" dan kerangka "Population, Intervention, Comparison and Outcome". Carian menyeluruh dilakukan di PubMed, Scopus dan Web of Science. Kajian yang layak merangkumi ujian terkawal rawak, ujian terkawal serta kajian kuasi-eksperimen melibatkan manusia atau haiwan dengan MSD yang dirawat menggunakan Moringa. Risiko bias dinilai menggunakan alat "Joanna Briggs Institute" dan "Systematic Review Centre for Laboratory Animal Experimentation". Sebanyak 16 kajian memenuhi kriteria inklusi (5 kajian manusia, 11 kajian haiwan). Moringa menunjukkan pengurangan kesakitan yang signifikan dalam kalangan manusia. [Skor "Visual Analogue Scale" (VAS) keletihan berkurang sebanyak 32.7, manakala skor VAS sakit sendi berkurang sebanyak 12] serta penanda keradangan seperti serum amyloid A, tumor necrosis factor-alpha dan interleukin-6. Kajian ke atas haiwan pula menunjukkan kesan analgesik yang kuat, termasuk pengurangan kejang sebanyak 83.66% dan pengurangan edema sebanyak 97.33% pada dos 500 mg/kg serta pengurangan tekanan oksidatif seperti malondialdehyde. Tiada toksisiti utama diperhatikan pada dos sehingga 2000 mg/kg. Kesimpulannya, Moringa berpotensi sebagai agen anti-radang, analgesik, dan antioksidan yang selamat untuk menyokong kesihatan muskuloskeletal. Namun, lebih banyak ujian klinikal yang berkualiti tinggi diperlukan untuk mengesahkan keberkesanan, menentukan dos optimum dan menjamin keselamatan penggunaan.

***Kata kunci**: Kelegaan kesakitan; keradangan; Moringa; perubatan alternatif; tekanan oksidatif*

ABSTRACT

Musculoskeletal disorders (MSDs) are a major public health concern, impairing mobility, productivity and quality of life. With a growing interest in functional foods and nutraceuticals, the *Moringa* species, widely consumed and rich in bioactive compounds, is being explored for its potential role in musculoskeletal health. However, its efficacy in MSD management remains unclear. This systematic review evaluates the safety and therapeutic potential of *Moringa* species in MSD management. Following the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Population, Intervention, Comparison and Outcome framework, comprehensive searches of PubMed, Scopus, and the Web of Science were conducted. Eligible studies included randomised controlled trials, controlled trials, and quasi-experimental studies involving human or animal models of MSDs treated with *Moringa* species. Risk of bias was assessed using the Joanna Briggs Institute and Systematic Review Centre for Laboratory Animal Experimentation tools. Altogether, 16 studies met the inclusion criteria (5 human trials and 11 animal studies). Moringa significantly reduced pain in humans [Visual Analogue Scale (VAS) score of fatigue decreased by 32.7, while VAS score of joint pain was reduced by 12] and inflammation markers such as serum amyloid A, tumour necrosis factor-alpha and interleukin-6. Animal studies demonstrated strong analgesic effects, including 83.66% writhing inhibition and 97.33% oedema reduction at 500 mg/kg and lower oxidative stress such as malondialdehyde. No major toxicity was observed at doses up to 2000 mg/kg. The *Moringa* species exhibits promising anti-inflammatory, analgesic and antioxidant properties, supporting their potential as safe functional foods or nutraceuticals for musculoskeletal health. However, well-designed clinical trials are needed to confirm its efficacy, optimised dosage and safety.
Keywords: Alternative medicine; inflammation; Moringa; oxidative stress; pain relief

INTRODUCTION

Musculoskeletal health is fundamental to mobility and daily functioning, relying on the coordinated performance of muscles, bones, joints and connective tissues. More than 150 conditions that affect this system are classified as musculoskeletal impairments, often resulting in temporary or long-term limitations in participation and physical function (Blyth et al. 2019). Musculoskeletal disorders (MSDs) represent a significant public health burden and are one of the leading causes of disability worldwide (World Health Organisation 2022). Common conditions such as osteoarthritis (OA), rheumatoid arthritis (RA), back pain and tendinitis contribute substantially to chronic pain, reduced mobility, and diminished quality of life (QoL). The 2019 Global Burden of Disease (GBD) analysis estimated that 1.71 billion people are affected by MSDs, with low back pain being the single largest contributor (Cieza et al. 2021). High-income countries report the greatest burden, followed by South-East Asia and the World Health Organisation (WHO) Western Pacific regions (Cieza et al. 2021). Beyond physical impairment, the chronic inflammation, pain and disability associated with MSDs have significant implications in mental health, social participation and productivity (Hartvigsen et al. 2018). With ageing populations and increased engagement in recreational and occupational physical activity, the prevalence of MSDs continues to rise (Anand et al. 2023).

Although lifestyle interventions, ergonomic optimisation and physical therapy are recommended as core components of MSD management, pharmacological approaches remain the primary treatment strategy (El-Tallawy et al. 2021). Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying antirheumatic drugs (DMARDs) are widely used to alleviate pain and inflammation (Benjamin et al. 2023; Ghlichloo & Gerriets 2023). However, prolonged use of these agents is frequently associated with gastrointestinal complications, cardiovascular and renal risks, and, in some cases, drug dependence (Chou et al. 2009; Fowler et al. 2014). These well-recognised adverse effects highlight the need for safer, effective and sustainable therapeutic options that can complement or potentially replace conventional pharmacotherapy in MSD management.

The *Moringa* genus, which comprises 13 species distributed across Southwest Asia, Northeast Africa, Southwest Africa and Madagascar has now gained growing scientific interest. Several species, including *Moringa oleifera*, *Moringa stenopetala*, *Moringa peregrina*,

Moringa drouhardii and *Moringa concanensis*, have been investigated for their medicinal value, with *M. oleifera* emerging as the most widely studied and utilised (Abd Rani et al. 2018). Known traditionally as the "drumstick tree" or "miracle tree," *M. oleifera* has been used in many regions for its nutritional, therapeutic and anti-inflammatory properties. Its leaves, seeds and pods are rich in vitamins A, C and E, as well as minerals such as calcium and potassium, and phenolics compounds (quercetin, kaempferol and chlorogenic acid) (Divya et al. 2024; Idris & Kumar 2024; Khan et al. 2022). These bioactive compounds contribute to its potent antioxidant, analgesic, anti-inflammatory and antimicrobial activities.

Evidence from preclinical studies suggests that moringa extracts may be beneficial for musculoskeletal health by modulating inflammatory pathways, reducing oxidative stress and supporting tissue repair. Moringa demonstrates the ability to downregulate cyclooxygenase-2 (COX-2), suppress pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) and inhibit signalling pathways associated with chronic pain and inflammation (Abd Rani et al. 2018; Divya et al. 2024; Pareek et al. 2023). Its strong antioxidant profile enables it to neutralise free radicals that contribute to oxidative damage within cartilage and joint tissues (Divya et al. 2024). Additionally, animal studies indicate that moringa may support bone health by enhancing collagen synthesis and promoting bone maintenance and repair (Liu et al. 2021).

Despite these promising findings, evidence specifically evaluating moringa for MSDs remains limited, scattered and methodologically heterogeneous, with substantial variations in species used, extraction methods, dosage and outcome measures. Although several reviews have addressed moringa's general medicinal properties, few have synthesised its relevance to MSDs (Abd Rani et al. 2018; Divya et al. 2024; Pareek et al. 2023). Key gaps persist regarding optimal dosing, long-term safety, mechanisms most relevant to musculoskeletal tissues, and how its effects compare with standard pharmacological therapies. Therefore, this systematic review aims to consolidate existing preclinical and clinical evidence on the safety and therapeutic potential of *Moringa* species for MSDs, providing clarity on its possible clinical applications and guiding future research.

MATERIALS AND METHODS

A systematic review was performed, focusing on the effects of *Moringa* species on arthritis and MSDs according to the research question: Can *Moringa* species produce beneficial effects on conditions related to MSDs? This report was based on the Population, Intervention, Comparison and Outcome (PICO) framework (Eriksen & Frandsen 2018), which comprised: (i) Population – MSD (humas of any age: child, adult, older people and animals); (ii) Intervention – *Moringa* species; (iii) Comparator – Placebo or the usual treatment for inflammation; and (iv) Outcome – Pain relief, analgesia, function, QoL, pain management, reduce soreness and beneficial health effects. This systematic review also met the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The study protocol was registered under PROSPERO (CRD42024612652).

Search Strategy and Selection Criteria

The search for English language articles published between the first inception of the articles and 2024 was performed using three databases (PubMed, Scopus and the Web of Science). Non-English articles were excluded due to constraints related to translation resources and to ensure accuracy in data extraction and interpretation. Search terms such as ("Moringa" OR "*Moringa oleifera*" OR "drumstick tree" OR "horseradish tree" OR "kelor") AND ("arthritis" OR " gout" OR "osteoarthritis" OR "rheumatoid" OR "lupus" OR "low back pain" OR "musculoskeletal" OR "joint" OR "muscle" OR arthralgia OR arthriti* OR analgesi*) AND (physical discomfort, analgesia) were used. The full search strings used

for the articles searched were listed in Table 1. All the searched articles were downloaded to the citation manager (EndNote, version 20, Clarivate, Philadelphia, PA, USA). Duplicated articles were removed using the automation tools and a manual search of the articles in the citation manager. The inclusion criteria for the study were as followed: (i) randomised controlled trial; (ii) controlled trial; and (iii) quasi-experimental before-and-after studies. Meanwhile, the exclusion criteria involved review papers and conference proceedings. Likewise, grey literature (e.g., theses, dissertations, reports and preprints) was not included because the focus of this review was on peer-reviewed, methodologically robust evidence. Excluding grey literature also ensured consistency in study quality and reduced the risk of including studies lacking adequate methodological reporting.

The titles and abstracts of the identified articles were then screened by independent reviewers (SA, SB and MR) according to the objective of the study. The selected studies were then chosen or excluded according to the inclusion and exclusion criteria set earlier. The final full-text articles were also assessed by the same reviewers. Any disagreement in the screening process was resolved by physical discussion with the involvement of other reviewers (NF, AMN and HA). All full-text publications and pertinent review articles were examined for additional studies through their references.

Data Extraction and Analysis

A premade, uniform data extraction form (Table S1) was used to collect the pertinent information from each unique article. Data acquisition for the human studies involved the following parameters: authors' names, year of publication, nation and location, study design, population and sample size under investigation, study goal, the type and dosage of moringa, laboratory analysis, sampling procedures for outcome measured, primary findings and primary statistical analyses. Meanwhile, data extracted from the animal studies comprised: authors' names, year of publication, nation and location, animal model, study design, population and sample size under investigation, study objectives, main findings, the kind and dosage of moringa, the duration of the experiment, laboratory analysis and sampling techniques for outcome measurement.

A meta-analysis was not conducted due to substantial heterogeneity across the included studies, including variations in the *Moringa*

TABLE 1: Search string for article search

Databases	Search String
PubMed	("Moringa"[All Fields] OR "*Moringa oleifera*"[All Fields] OR "drumstick tree"[All Fields] OR "horseradish tree"[All Fields] OR "kelor"[All Fields]) AND ("athritis"[All Fields] OR "gout"[All Fields] OR "osteoarthritis"[All Fields] OR "rheumatoid"[All Fields] OR "lupus"[All Fields] OR "pain"[All Fields] OR "musculoskeletal"[All Fields] OR "joint"[All Fields] OR "muscle"[All Fields] OR ("arthralgia"[MeSH Terms] OR "arthralgia"[All Fields] OR "arthralgias"[All Fields]) OR "arthriti*"[All Fields] OR "analgesi*"[All Fields] OR ("edema"[MeSH Terms] OR "edema"[All Fields] OR "swelling"[All Fields] OR "swell"[All Fields] OR "swelled"[All Fields] OR "swellings"[All Fields] OR "swells"[All Fields]))
Scopus	TITLE-ABS-KEY(("Moringa" OR "*Moringa oleifera*" OR "drumstick tree" OR "duzigarzan" OR "horseradish tree" OR "benzoilbaumin German" OR "kelor") AND ("athritis" OR "gout" OR "osteoarthritis" OR "rheumatoid" OR "lupus" OR "low back pain" OR "musculoskeletal" OR "joint" OR "muscle"))
Web of Science	ALL= (("Moringa" OR "*Moringa oleifera*" OR "drumstick tree" OR "duzigarzan" OR "horseradish tree"OR "benzoilbaumin German" OR "kelor") AND ("athritis" OR "gout" OR "osteoarthritis" OR "rheumatoid" OR "lupus" OR "low back pain" OR "musculoskeletal" OR "joint" OR "muscle"))

species used, extract preparation, dosage, intervention duration, outcome measures and study designs. These differences prevented meaningful statistical pooling and justified the use of a narrative synthesis approach.

Quality Assessment

Two independent reviewers (NB and NN) conducted quality assessments, and any disagreements were settled by consensus. The inclusion or exclusion of studies did not involve the quality assessment findings. Checklists created using the Joanna Briggs Institute (JBI) critical appraisal tools – checklist for randomised controlled trials (Munn et al. 2020), which included 13 evaluation criteria performed on each included study, were utilised to evaluate the human-controlled trial research. The evaluation of animal studies was conducted using Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE)'s risk of bias tool for animal studies (Zhang et al. 2019), which involved ten evaluation criteria for quality assessment.

RESULTS

A total of 611 articles were identified during the initial screening using a combination of keywords. After excluding 161 duplicated studies, 428 articles were further excluded based on the following: irrelevant titles and abstracts, not recent publications (more than 5 years), different study populations and not original research (reports/review articles and proceedings). Of the 22 full-text articles assessed, 14 studies were included. The addition of 2 studies from previous reviews yielded 16 studies for the final synthesis. Figure 1 displayed the flowchart of the search results according to PRISMA.

A total of 16 articles underwent critical appraisal for this review, comprising 6 cross-sectional studies and a mixed-method study. The quality of the cross-sectional studies was assessed using the Critical Appraisal Tools for Checklist for Randomised Control Trial from JBI, while the animal study was evaluated using SYRCLE's risk of bias tool. Based on the quality appraisal results, all 16 articles met the criteria and were deemed suitable for this review. Table 2a and Table 2b listed the data on critical appraisal of the included sources of evidence.

Table 3a and Table 3b presented the effects of *Moringa* species on musculoskeletal-related disorders, drawn from 16 articles, with 11 focusing on nonclinical studies and 5 on clinical trials. Most of the studies were conducted in Asia (n = 11), followed by Africa (n = 2), North America (n = 2) and South America (n = 1). The studies primarily utilised extracts instead of isolated compounds from moringa. Subsequently, the solvents employed included aqueous solutions, ethanol, methanol, ethyl acetate fractions and chloroform. Extraction using aqueous or hydro alcohol-based methods yielded the highest results in the extract preparation. The outcomes of the studies primarily concentrate on anti-arthritic, anti-inflammatory, anti-nociceptive, osteogenic activity, fatigue relief and toxicity levels.

Main Findings in Human Studies

The findings from human studies were shown in Table 4. This section summarised the effects of *M. oleifera* on MSDs, focusing on three key themes: pain and discomfort, anti-inflammatory and oxidative stress markers, and other potential benefits like mobility, sleep quality and mood.

Several studies evaluated the effects of interventions on pain. This theme emerged as the most critical outcome for individuals with MSDs. Abe et al. (2023) reported reductions in stiff shoulder/neck pain, joint pain and other muscle pain based on the Visual Analogue Scale (VAS). The reductions in joint pain by 12, stiff shoulder/neck pain by 32.7 and muscle pain by 18 were all statistically significant (Singh et al. 2011). Similarly, Singh et al. (2011) demonstrated significant reductions in pain by 2.73 using the pain scale. Celetaria et al. (2017) reported substantial reductions in pain at various time points post-application, with decreases documented immediately post-application by

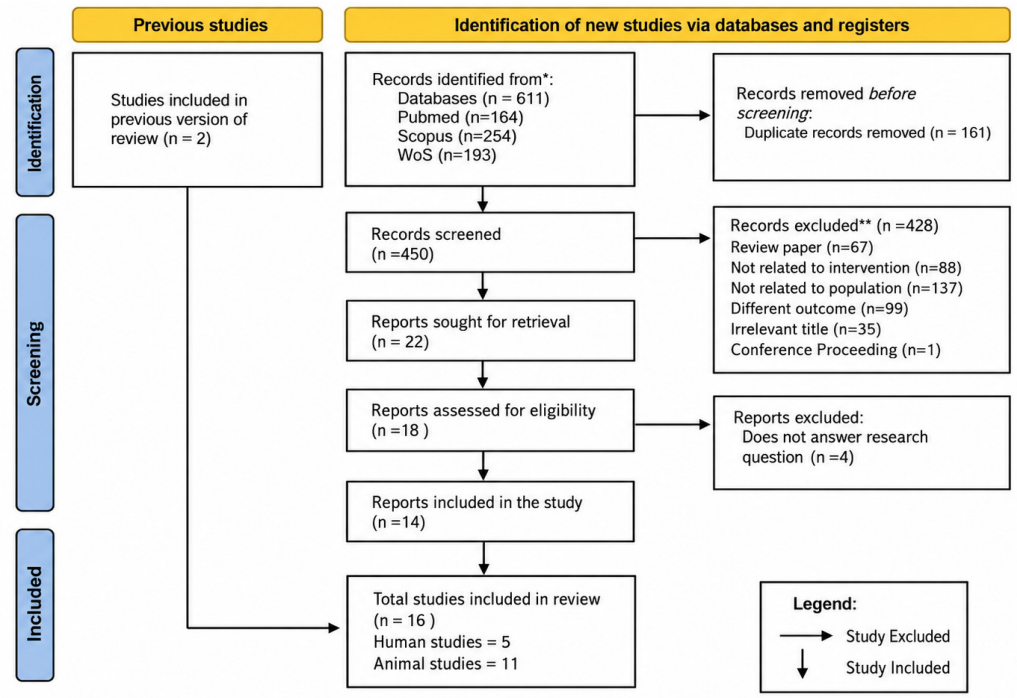

FIGURE 1: Preferred Reporting Item for Systematic Review and meta-analysis (PRISMA) flow diagram

4.63, 30 minutes post-application by 15.57 and 1-hour post-application by 23.78 (Celetaria et al. 2017). Another study highlighted that low back pain was also reduced by 35 (Shimizu et al. 2019).

The reduction of inflammatory and oxidative stress markers was another important theme. Abe et al. (2023) reported reductions in oxidative stress markers, including 8-isoprostaglandin F2α (8-iso-PGF_2t) and 8-hydroxy-2-deoxyguanosine (8-OHdG). Although the increase in 8-iso-PGF_2t levels in the moringa supplementation group was small at 0.1 ng/mg Cre and not statistically significant, the difference compared to the placebo group, which showed an increase of 0.4 ng/mg Cre, was statistically significant. The reduction in 8-OHdG levels was not significant in either group, with the moringa group showing a reduction of 0.2 ng/mg Cre and the placebo group showing a reduction of 0.5 ng/mg Cre (Abe et al. 2023). Similarly, Nugroho et al. (2023) demonstrated that the addition of *M. oleifera* to standard therapy significantly reduced inflammatory markers, such as serum amyloid A (SAA), decreasing by 31.8 ng/ml compared to 19.75 ng/ml standard therapy alone. However, the comparison group in their study did not show a significant reduction in inflammatory markers with a decrease of only 12.06 (Nugroho et al. 2023).

The studies also reported additional benefits beyond pain and inflammation, including swelling, tenderness, fatigue, mobility, sleep quality and mood improvement. Singh et al. (2011) observed significant improvements in swelling by mean score of 2.73, tenderness by 2.00 and mobility scores by 1.91, suggesting enhancements in physical functionality and independence. Two studies gave significant results on the effect of moringa on fatigue, with Shimizu et al. (2019) reporting significant reductions in fatigue by 42, while Abe et al. (2023) documented fatigue reduction of 32.7. Abe et al.

TABLE 2a: Critical appraisal of included sources of evidence (Human studies)

Author (Year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Risk of Bias
Abe et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Nugroho et al. (2023)	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Singh et al. (2011)	Y	U	Y	N	N	Y	Y	Y	U	Y	Y	Y	U	Moderate
Celetaria et al. (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Shimizu et al. (2019)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Moderate

Y: Yes; N: No; U: Unclear

Q1: Was true randomisation used for assignment of participants to treatment groups?; Q2:Was allocation to treatment groups concealed?; Q3: Were treatment groups similar at the baseline?; Q4: Were participants blind to treatment assignment?; Q5: Were those delivering the treatment blind to treatment assignment?; Q6: Were treatment groups treated identically other than the intervention of interest?; Q7: Were outcome assessors blind to treatment assignment?; Q8: Were outcomes measured in the same way for treatment groups?; Q9: Were outcomes measured in a reliable way; Q10: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?; Q11: Were participants analysed in the groups to which they were randomised?; Q12: Was appropriate statistical analysis used?; Q13: Was the trial design appropriate and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

TABLE 2b: Critical appraisal of included sources of evidence (Animal studies)

Author (Year)	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other (External funding or conflict interest)	Risk of Bias
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	
Adedapo et al. (2015)	U	Y	U	Y	U	U	U	Y	Y	Y	Moderate
Fatima & Fatima (2016)	U	Y	U	U	U	U	U	Y	Y	Y	Moderate
Kumar et al. (2013)	Y	Y	U	U	N	U	N	Y	Y	Y	Moderate
Mahajan et al. (2007)	Y	Y	U	U	N	U	N	Y	Y	Y	Moderate
Mahdi et al. (2018)	Y	Y	U	U	N	U	Y	Y	Y	Y	Moderate
Martínez-González et al. (2017)	U	Y	U	U	Y	U	Y	Y	Y	Y	Moderate
Palomino-Pacheco et al. (2024)	U	Y	U	U	Y	U	Y	Y	Y	Y	Moderate
Sailaja et al. (2022)	U	Y	U	U	Y	U	Y	Y	Y	Y	Moderate
Saleem et al. (2020)	U	Y	U	U	Y	U	Y	Y	Y	Y	Moderate
Shamlan et al. (2021)	U	Y	U	U	N	U	Y	Y	Y	Y	Moderate
Tamrat et al. (2017)	U	Y	U	U	N	U	Y	Y	Y	Y	Moderate

Y: Yes; N: No; U: Unclear

Q1: Sequence generation; Q2: Baseline characteristics; Q3: Allocation concealment; Q4: Random housing; Q5: Blinding of caregivers and/or investigators; Q6: Random outcome assessment; Q7: Blinding of outcome assessors; Q8: Incomplete outcome data; Q9: Selective outcome reporting; Q10: Other sources of bias

TABLE 3a: Characteristics of included studies (Clinical studies)

No	Author (Year)	Study Location	Study Population	Type of Study	Intervention and Control Group	Study Objective/ Outcome
1.	Abe et al. (2023)	Japan	Healthy adult males and females, involving 140 participants	Randomised, double-blind, placebo-controlled, and parallel-group trial	Intervention group: Received Moringa Seed Extract (MSE) tablets containing 12 mg glucomoringin daily for 4 weeks. Control group: Placebo tablets, containing dextrin as substitute	• Fatigue-associated physical discomfort • Sleep quality improvement
2.	Nugroho et al. (2023)	Indonesia	42 patients with diagnosis of Rheumatoid Arthritis following ACR/EULAR criteria	Double-blind randomised controlled trial	Intervention group: Standard therapy with methotrexate (7.5 mg/week) + *Moringa oleifera* leaf extract (500 mg capsules, administered twice daily for 28 days). Control group: Standard therapy with methotrexate (7.5 mg/week)	Change in serum amyloid A (SAA) levels, measured using the ELISA method
3.	Singh et al. (2011)	India	44 patients with mandibular fractures, specifically those with associated undisplaced maxillary or zygomatic complex fractures	Randomised, paralled and placebo-controlled trial	Intervention group: • Group 1: Osteoseal • Group 2: *Moringa oleifera* • Group 3: Harjor (*Cissus quadrangularis*) Control group: Placebo	Assessment of: • Fracture healing. • Pain, swelling, tenderness, and mobility of fractured segments at weeks 1, 4, and 6. • Pre- and post-treatment serum calcium (total and ionic) and phosphorus levels.
4.	Celetaria et al. (2017)	Philippines	60 participants involving those who self-reported arthritic pain and medically diagnosed with osteoarthritis and/or rheumatoid arthritis patients	Randomised, parallel, not blinded trial	Intervention group: Received both pharmacologic and adjunct topical application of Malunggay seeds oil extract. Control group: Received prescribed pharmacologic treatment	Pain reduction
5.	Shimizu et al. (2019)	Japan	40 healthy adult working men and women aged 30-64 years	Randomised, parallel, double-blind, and placebo-controlled trial	Intervention group: Daily oral intake of moringa seed extract tablets (120 mg of moringa seed extract). Control group: Placebo tablet (containing dextrin as substitute)	Reduction in fatigue (anti-fatigue effect of moringa)

TABLE 3b: Characteristics of included studies (Non-clinical studies)

No	Author (Year)	Study Location	Study Population	Intervention and Control Group	Study Objective/ Outcome
1.	Adedapo et al. (2015)	Nigeria	Sample size: 150; Disease model: Induced (experimental) models • Rats: 80 healthy female white Wister strain albino rats weighing between 100-160 g • Mice: 70 female mice weighing between 20-30 g	Five animals/ group (total six groups for each - experimental, control and acute toxicity test)	Analgesic, anti-inflammatory, anti-oxidant, phytochemical and toxicological properties of *Moringa oleifera*
2.	Fatima & Fatima (2016)	India	Sample size: 36; Disease model: Induced (experimental) models Healthy adult rats of Albino Wistar strain weighing between 150 g and 250 g	Intervention group: Treated with ethanolic (250 mg/kg and 500 mg/kg) and aqueous (500 mg/kg) leaf extracts of *Moringa oleifera* Control group: Diclofenac sodium (10 mg/kg, intraperitoneally) and negative control for comparison	Anti-arthritic activity of ethanolic and aqueous leaf extracts of *Moringa oleifera*
3.	Kumar et al. (2013)	India	Sample size: 30; Disease model: Induced (experimental) models Swiss albino rats (Wistar strain, 150-200g)	Intervention group: Received different doses (125, 250, 500 mg/kg, p.o) of methanolic extracts of *Moringa oleifera* Control group: standard drug aspirin (100 mg/kg p.o.) and vehicle for comparison	Antiarthritic effect of stem bark from *Moringa oleifera*
4.	Mahajan et al. (2007)	India	Sample size: 30; Disease model: Induced (experimental) models Adult female Wistar Rats, weighing 150-180g	Intervention group: Received different doses (100 and 200 mg/kg/day per os) of ethanolic extract of *Moringa oleifera* Control group: No treatment, and the reference standard (dexamethasone 5 mg/kg body weight/day per os)	Anti-inflammatory and anti-arthritic properties.
5.	Mahdi et al. (2018)	Malaysia	Sample size: 30; Disease model: Induced (experimental) models Healthy Sprague-Dawley male rats, 8-10 weeks old and weighing 150-200g	Intervention group: Treated with ethanol extract of *Moringa oleifera* leaves at 250 and 500 mg/kg/day Control group: One group received indometachin (2.5mg/kg/day), Another group not receiving the moringa extract; disease progression was monitored without intervention	Anti-arthritic and anti-nociceptive effects of *Moringa oleifera* leaves

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No	Author (Year)	Study Location	Study Population	Intervention and Control Group	Study Objective/ Outcome
6.	Martínez-González et al. (2017)	Mexico	Sample size: 12; Disease model: Induced (experimental) models Male and female wistar rats weighed 180-200g	Intervention group: Rats treated with *Moringa oleifera* leaves extracts at doses ranging from 30 to 300 mg/kg Control group: Received no *Moringa oleifera* treatment served as the baseline for comparison. Positive control received drugs such as naproxen, ketorolac or dexamethasone	Antinociceptive (pain-relieving) and anti-inflammatory activities of *Moringa oleifera* leaf extracts
7.	Palomino-Pacheco et al. (2024)	Peru	Sample size: 79; Disease model: Induced (experimental) models 20 female rats of 160 ± 10 g body weight and 20 male rats of 170 ± 10 g body weight	Intervention group: Treated with *Moringa oleifera* aqueous extract at doses of 100 mg/kg, 250 mg/kg and 500 mg/kg daily. Control group: No extract or only vehicle treatment. Comparative group received an acute oral toxicity test (2000 mg/kg in a single dose) and repeated-dose toxicity test for 28 days at the intervention doses.	• Anti-inflammatory, antihyperuricaemic, and analgesic effects in gout • Oral toxicity of *Moringa oleifera* leaf aqueous extract
8.	Sailaja et al. (2022)	United States of America	Sample size: 18; Disease model: Induced (experimental) models 18 C57BL/6 male mice	Intervention group: Treated with MIC-1 (80 mg/kg) daily for three days. Control group: No treatment	Anti -inflammatory effects of moringa isothiocyanate-1 (MIC-1) extracted from seeds of *Moringa oleifera* Lam
9.	Saleem et al. (2020)	Pakistan	Sample size: 12; Disease model: Induced (experimental) models 12 Wistar rats of either sex, weighing 150-200g	Intervention group: Treated with *Moringa oleifera* extracts (methanolic, aqueous, and ethyl acetate) at doses of 150 mg/kg, 300 mg/kg and 600 mg/kg. Control group: Treated with a vehicle solution or no treatment.	Anti-arthritic potential of *Moringa oleifera* (wild type).
10.	Shamlan et al. (2021)	Saudi Arabia	Sample size: 25; Disease model: Induced (experimental) models 25 adult male Wistar albino rats, which weighed 160–190 g and aged 5–6 weeks	Intervention group: Treated with 0.5 g of moringa leaves, 1 ml of moringa seed oil and combined Moringa leaves and seed oil. Control group: Arthritic induced rat and non-arthritic rat, both with no treatment	Effect of Moringa peregrina on rheumatoid arthritis and other inflammations

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No	Author (Year)	Study Location	Study Population	Intervention and Control Group	Study Objective/ Outcome
11.	Tamrat et al. (2017)	Ethiopia	Sample size: 90; Disease model: Induced (experimental) models 90 mice of Healthy Swiss albino mice (6–8 weeks old, 25–35 g)	Intervention groups: Treated with solvent fractions of *Moringa stenopetala* leaves (chloroform, methanol, and aqueous fractions) at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg. Control groups: Treated with morphine (20 mg/kg) or aspirin (100 mg/kg or 150 mg/kg) based on the respective models, and another group treated with 10 mL/kg of vehicles (distilled water or 2% Tween 80).	Analgesic and anti-inflammatory activity of the solvent fractions of *Moringa stenopetala*

ACR: American College of Rheumatology; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; ELISA: enzyme-linked immunosorbent assay; MSE: Moringa seed extract; MIC-1: Moringa isothiocyanate-1; RA: Rheumatoid arthritis; p.o.: per os (oral administration); mg: milligram; kg: kilogram; mL: millilitre; g: gram

(2023) also highlighted improved sleep quality, with a significant difference observed compared to the placebo group using the Profile of Mood States (POMS-2). Additionally, Abe et al. (2023) evaluated mood improvements; nevertheless, the findings were not statistically significant. These outcomes suggest that *M. oleifera* supplementation may offer broader benefits for the well-being of patients with musculoskeletal disease (Abe et al. 2023).

Main Findings in Animal Studies

The findings from animal studies using various methods to measure the therapeutic effect of *Moringa* species in musculoskeletal disease were shown in Table 5. Key findings were summarised into analgesic effect, anti-inflammatory effect, antioxidant effect, effect on body weight and toxicology.

(i) Analgesic effect

Adedapo et al. (2015) demonstrated that moringa extracts at 200 mg/kg significantly reduced pain, as indicated by a decrease in writhing counts (4.5 ± 4.4 vs. 46.3 ± 21.8 in controls) and the paw lick counts by 47.4% in formalin tests. Similar findings by Martínez-González et al. (2017) using the formalin test demonstrated that both hexane and ethanol extracts of moringa reduced pain in the neurogenic and inflammatory phases, with the hexane extract showing superior efficacy at lower doses (30 mg/kg), achieving significant reductions in flinching behaviour. In contrast, ethanol extract required higher doses to show comparable results (Martínez-González et al. 2017). Another study involved the paw pressure test, which revealed that ethanol extracts reduced hyperalgesia significantly, achieving comparable results to standard drugs like ketorolac (Martínez-González et al. 2017). Similarly, Tamrat et al. (2017) reported that the aqueous fraction of moringa (400 mg/kg) showed the highest protection against pain, achieving 73.6% inhibition in the tail-flick test and 58% inhibition in the writhing test, surpassing standard drugs

TABLE 4: Main findings on human studies

Author	Tools	Outcome	Result Value
Abe et al. (2023)	A. Fatigue and discomfort -VAS	1. Fatigue 2. Stiff shoulder/neck pain 3. Joint pain 4. Muscle pain	1. Fatigue: ↓ 32.7, (p = 0.041) 2. Stiff shoulder/neck pain ↓ 32.7 (p = 0.041). 3. Joint pain: ↓ 12 (p = 0.013). 4. Muscle pain: ↓ 18 (p = 0.044).
	B. Sleep quality- POMS-2	Sleep quality	↑ compared to placebo (p<0.05).
	C. Anti- inflammatory markers- ELISA	Oxidative Stress 1. 8-iso-PGF_2t levels 2. 8-OHdG levels	8-iso-PGF_2t (ng/mg Cre) - MSE group: ↑ 0.1 (p = 0.092). - (MSE vs placebo): ↑ 0.4 (p = 0.031). 8-OHdG (ng/mg Cre) - MSE group: ↓ 0.2 (p = 0.752). - Placebo group): ↓ 0.5 (p not significant).
	D. Mood-POMS-2	Mood	Improved mood but no significant difference MSE vs placebo (p > 0.05).
Nugroho et al. (2023)	A. Anti-inflammatory markers-ELISA	Inflammatory Marker (SAA)	Standard therapy: ↓ 19.75. Standard therapy + *M. oleifera*: ↓ 31.8 (p = 0.01).
	B. Anti-inflammatory markers-ELISA (comparison group)	Combination Therapy Effect	↓ 12.06 (p = 0.26, not significant).
Singh et al. (2011)	A. Pain and swelling-Pain scales	Pain and swelling	Pain: ↓ 2.73 (p < 0.001). Swelling: ↓ 2.73 (p < 0.001).
	B. Tenderness and mobility - Tenderness and mobility scales	Tenderness and Mobility	Tenderness: 2.00 (p < 0.001). Mobility: 1.91 (p < 0.001).
Celetaria et al. (2017)	Pain - VAS	Pain	Immediately post-application: ↓ 4.63 (p = 0.001). 30 minutes post-application: ↓15.57 (p = 0.001). 1 hour post-application: ↓ 23.78 (p = 0.001).
Shimizu et al. (2019)	Fatigue-VAS	Fatigue	Fatigue: ↓ 42 (p < 0.001).
	Low back pain-VAS	Pain	Low back pain: ↓ 35 (p < 0.05).

Cre: Creatinine; ELISA: Enzyme-linked immunosorbent assay; MSE: Moringa seed extract; mg: milligram; ng: Nanogram; POMS-2: Profile of Mood States-2; SAA: Serum amyloid A; VAS: Visual analogue scale 8-iso-$PGF_2\alpha$: 8-iso-prostaglandin F2α; 8-OHdG: 8-hydroxy-2′-deoxyguanosine

of morphine and aspirin. Palomino-Pacheco et al. (2024) also reported that in acetic acid-induced writhing tests, moringa extract at 500 mg/kg showed 83.66% inhibition of writhing, closely comparable to tramadol, which achieved 89.92%. Additionally, Mahdi et al. (2018) noted dose-dependent analgesic effects using thermal tests, with significant improvements in latency times at 250, 500 and 750 mg/kg doses. The 500 mg/kg dose exhibited superior pain mitigation compared to 250 mg/kg and was comparable to indomethacin (Mahdi et al. 2018).

(ii) Anti-inflammatory effect

Moringa extracts were effective in reducing oedema in various models. Fatima and Fatima (2016) observed significant paw oedema reduction using ethanolic (500 mg/kg) and aqueous (500 mg/kg) extracts, achieving up to 88.64% inhibition with moringa compared to the standard treatment of diclofenac sodium at 86.36% inhibition. Kumar et al. (2013) reported dose-dependent oedema inhibition, with 500 mg/kg moringa reducing inflammation by 97.33% compared to standard treatment of aspirin, which reduced inflammation by 95.55%. Saleem et al. (2020) reported a maximum inhibition of 82.28% at 600 mg/kg, which outperformed piroxicam. By measuring paw oedema, Adedapo et al. (2015) found that moringa extracts significantly reduced oedema using carrageenan and histamine tests, with more rapid mean paw thickness reductions at 100 mg/kg/day within 1 hour after carrageenan injection. The findings of the histamine test showed the highest reduction at 200 mg/kg/day after a 2-hour injection of histamine (Adedapo et al. 2015).

Martínez-González et al. (2017) reported that in the carrageenan-induced paw oedema model, the ethanol extract of moringa exhibited dose-dependent anti-inflammatory activity, with a maximum reduction of 86.2% at 300 mg/kg. Another study observing paw oedema demonstrated significant inhibition of paw oedema with aqueous and methanol fractions, particularly at higher doses (400 mg/kg) (Tamrat et al. 2017). These fractions were effective in mitigating inflammatory reactions, comparable to or better than standard drugs like aspirin (Tamrat et al. 2017). This result was significantly higher than the vehicle control and comparable to the standard anti-inflammatory drug naproxen (Tamrat et al. 2017). Mahajan et al. (2007) observed that *M. oleifera* ethanol extract (MOEE) significantly reduced paw oedema volumes and arthritis scores.

The only animal study observing the effect of uric acid in gouty arthritis with moringa was by Palomino-Pacheco et al. (2024). They revealed that in monosodium urate-induced arthritis models, moringa extract at 500 mg/kg significantly reduced ankle swelling and inflammatory cell infiltration, indicating its efficacy in mitigating gout-like inflammation.

Sailaja et al. (2022) reported that moringa extract (MIC-1) demonstrated significant suppression of inflammatory markers in skeletal muscle, including reductions in TNF-α, IL-1β and IL-6 expression by 60% to 80% in treated groups. The study also found that MIC-1 reduced nitric oxide production and suppressed the activation of inflammatory pathways, as evidenced by reduced nuclear translocation of NF-κB and downregulation of over 1,000 inflammation-related genes (Sailaja et al. 2022).

In a study involving inflammatory markers, Mahajan et al. (2007) reported that inflammatory cytokines such as TNF-α, IL-1 and IL-6, were substantially decreased at 200 mg/kg/day moringa extract, comparable to dexamethasone. Additionally, Saleem et al. (2020) reported that moringa extracts significantly reduced inflammatory markers including IL-6, IL-1β and TNF-α. Shamlan et al. (2021) used two forms of moringa, dried leaves and oil to assess their effectiveness towards inflammatory markers. It was found that moringa oil provided a substantial reduction in the inflammatory markers of IL-6 and TNF, followed by a combination of moringa oil and dried leaves (Shamlan et al. 2021). Moringa dried leaves, when used alone are less effective (Shamlan et al. 2021).

Several studies also observed the haematological profile. Kumar et al. (2013) reported that moringa extracts significantly improved red blood cell (RBC) count and haemoglobin (Hb) levels at 100 mg/kg and 250 mg/kg doses when compared to the control, while the positive results were comparable to aspirin-treated groups. The study also found that erythrocyte sedimentation rate (ESR), an indicator of systemic inflammation showed substantial improvement across treatment groups (Kumar et al. 2013). Similarly, Mahdi et al. (2018) reported that the 250 mg/kg dose of moringa extracts restored RBC count and haemoglobin levels to

TABLE 5: Main findings on animal studies

Bil	Author	Tools	Outcome	Result
1	Adedapo et al. (2015)	• Writhing test • Paw lick test	Pain	↓ writhes significantly by treatment group (methanolic extract of moringa) compared to the control group and indomethacin group • 90.3% reduce number of writhes by 200 mg/kg methanolic extract moringa • 83.8% reduce number of writhes by 100 mg/kg methanolic extract moringa • 78.9% reduce number of writhes by 50 mg/kg methanolic extract moringa • 78.9% reduce number of writhes by 10 mg/kg indomethacin ↓ licking time significantly by methanolic extract of moringa compared to the control group and indomethacin group
		Carrageenan and histamine test	Oedema formation	↓ edema effect in all treatment group of methanolic extract moringa compared to control group - carageenan induced • 50 mg/kg was highest reduction at 2 hour after carrageenan injection • 100 mg/kg was highest reduction at 1 h after carrageenan injection • 200 mg/kg was highest reduction at 3 h after carrageenan injection - histamine induced • 50 mg/kg was highest reduction at 3 h after histamine administration • 100 mg/kg was highest reduction at 3 h after histamine administration • 200 mg/kg was highest reduction at 2 h after histamine administration
		DPPH assay - Potential scavenger radical	Antioxidant effect	↑ antioxidant effect in 10 mg and 20 mg extracts of moringa (higher in 20 mg)
		Toxicological assessment	Toxicological	Safe dose (up to 800 mg/kg)
2	Fatima & Fatima (2016)	Plethysmometer and screw gauge	Oedema formation	↓ paw edema significantly in both ethanolic (500 mg/kg) and aqueous (500 mg/kg) extracts of MO • 86.36% inhibition of standard diclofenac sodium 10 mg/kg • 70.44% inhibition of MOET 250 mg/kg • 81.82% inhibition of MOET 500 mg/kg • 88.64% inhibition of MOET 500 mg/kg ↓ paw thickness significantly in Group 3 (diclofenac sodium), Group 5 (500 mg/kg of ethanolic extract of MO), and Group 6 (500 mg/kg of aqueous extract of MO) • 87.98% inhibition of standard diclofenac sodium 10mg/kg • 68.64% inhibition of MOET 250 mg/kg • 73.18% inhibition of MOET 500 mg/kg • 82.73% inhibition of MOET 500 mg/kg

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Bil	Author	Tools	Outcome	Result
		Visual arthritis scoring system	Improved arthritis score	↓ arthritis scores significantly in aqueous extract (500 mg/kg) and diclofenac sodium group. • Group 3 - diclofenac sodium 10 mg/kg, • Group 5 - 500 mg/kg of an ethanolic extract of MO • Group 6 - 500 mg/kg of aqueous extract of MO on the day 10
		ELISA	Improved CRP	↓ CRP level in serum samples • Group 3 - diclofenac sodium (7.47 mg/mL) • Group 5 - 500 mg/kg of ethanolic extract of MO (8.06 mg/mL) • Group 6 - 500 mg kg of aqueous extract of MO (7.65 mg/mL)
		Histopathology	Histopathology	Regeneration of cartilage and new bone formation
		Toxicological assessment	Toxicological	Safe dose (up to 2000 mg/kg)
3	Kumar et al. (2013)	Oedema formation (micrometre)	Oedema formation	↓ Percentage of inhibition of paw oedema with moringa as compared to the control group. It has an equivalent effect between moringa and aspirin. The findings as below: • Control - no reduction • MO (125 mg/kg) - 70.25% • MO (250 mg/kg) - 90.46% • MO (500 mg/kg) - 97.33% • Aspirin (100 mg/kg) - 95.55%
		Hematological analysis	Improved RBC count	The total RBC count is significantly improved with MO at 100 mg/kg and 250 mg/kg and Aspirin 100 mg/kg as compared to control group.
		Acute toxicity studies	Toxicology	Safe dose (up to 2000 mg/kg)
		Weighing scale	Increase body weight	↑ Body weight in different dose of MO and aspirin group. Increase as follows: a) MO (125 mg/kg) + 15 kg b) MO (250 mg/kg) + 17.7 kg c) MO (500 mg/kg) + 24.2 kg d) Aspirin (100 mg/kg) + 23.8 kg ↓ Weight in arthritic control -28.4 kg
		Visual arthritis scoring system	Reduced arthritis score	At Day 21, the MO at different dose and aspirin showed arthritic index significantly as compared to arthritic control

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No.	Author	Tools	Outcome	Result
4.	Mahajan et al. (2007)	Anti-inflammatory market (ELISA)	Reduced cytokines (IL, TNF)	• TNF-α, IL-1 were significantly in treatment group MO2 (200 mg/kg/day) and dexamethasone •↓ IL-6 in treatment group of MO2 • MO1 (100mg/kg/day) did not produce any effect on IL-1 and IL-6 level
		Westergen method for ESR	Reduced ESR	↓ ESR were significant in both doses of MO and dexamethasone ($p < 0.001$).
		Plethysmometer	Oedema formation	• In all treatment groups of MO1-, MO2- and dexamethasone, there is a highly significant reduction in edema formation ($p < 0.001$) on day 5 for primary lesions. • Secondary lesion of edema formation was significantly ↓ in all treatment groups of MO1-, MO2- and dexamethasone on day 21 ($p < 0.001$)
		Arthritic Index score	Reduced arthritis score	↓ Arthritic index scores of treatment groups significantly compared to the disease control group ($p < 0.01$).
		Spectrophotometer	Anti-oxidant properties	• Malondialdehyde (MDA) levels were significantly improved in MO1 and MO2 treatment groups ($p < 0.001$) and value is comparable with treatment groups with dexamethasone. • SOD and CAT activities were significantly reduced compared to diseased controls, approaching levels in non-arthritic rats
		Weighing scale	Reduced body weight	↓ Weight was significantly lower in both MO at 2 different dose of 100 mg/kg and 200 mg/kg as compared to diseased control ($p < 0.001$)
		Heamotoxylin and Eosin (H&E) stain	Histopathology	Synovial sections from MO1, MO2 and dexamethasone treated rats showed protection from the arthritic changes of bone destruction, cartilage erosion, severe angiogenesis and infiltration of lymphocytic cells.
5	Mahdi et al. (2018)	Wintrobe method	Improved ESR	ESR significantly improved in all treatment groups Moringa extract 250, 500 mg/kg and indomethacin ($p < 0.05$)
		Digital Micrometre	Oedema formation	• Moringa extract at 2 doses (250 and 500 mg/kg) and indomethacin significantly ↓ edema formation against diseased control groups, $p < 0.001$ and $p < 0.005$. • Moringa at 250 mg/kg exhibit highest percentage of inhibition especially in chronic phase, 70.80%, higher than indomethacin 70.48%
		Weighing scale	Increased body weight	• The moringa extract of 250 mg/kg dose significantly ↑ body weight ($p < 0.05$) while moringa extract at 500 mg/kg and indomethacin effect in increasing weight are not significant compared to the diseased control group.

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No.	Author	Tools	Outcome	Result
		Arthritic Index score	Reduced arthritis score	Both doses of moringa significantly ↓ arthritic index scores ($p < 0.05$), however moringa extract at 250 mg/kg showed better arthritic index
		Hematology Analyser (Beckman Coulter)	Improved RBC, Hb	RBC and Hb were restored to near-normal levels in treatment groups, with the moringa extract at 250 mg/kg dose performing best ($p < 0.05$).
		Walking Track Analysis	Preserved gait	The functional Index (FI) showed normal value for all treatment group and was abnormal in arthritis-induced control group
		Eddy's hot plate and tail flick	Pain	• Significant improvements in moringa extract of 250, 500, and 750 mg/kg doses ($p < 0.05$, $p < 0.001$) • Anti-nociceptive effect starts at 90 minutes with moringa extract, reached its peak at 180 minutes, while indomethacin effect starts at 60 minute and reached its peak at 120 minute • In CFA-induced rats, the 500 mg/kg dose showed superior pain mitigation compared to 250 mg/kg and indomethacin ($p < 0.05$, $p < 0.001$).
6	Martínez-González et al. (2017)	Formalin-induced nociception - observation of flinching	Pain	• Hexane Extract: Significant ↓ for neurogenic phase (73.3 ± 20.0 at 30 mg/kg; $p < 0.001$) and inflammatory phase (211.3 ± 47.9; $p < 0.001$), comparable to naproxen at 10 mg/kg. • Ethanol Extract: ↓ at higher doses; neurogenic phase (134.2 ± 20.5 at 30 mg/kg; $p < 0.001$), inflammatory phase (490.4 ± 38.2). Significant effects but lower efficacy compared to naproxen. Ethanol Extract: Significant ↓ in hyperalgesia: 68.0 ± 24.3% at 100 mg/kg and 48.5 ± 10.6% at 300 mg/kg. Comparable to ketorolac (76.8 ± 4.6%) and dexamethasone (30.0 ± 6.9%).
		Plethysmometer - Carrageenan-induced paw oedema	Oedema formation	• Ethanol Extract: Dose-dependent ↓ in inflammation: 74.3 ± 11.5% (100 mg/kg), 86.2 ± 5.7% (300 mg/kg). Significant vs. vehicle ($p < 0.05$). Naproxen (10 mg/kg) reduced inflammation to 36.9 ± 5.6%. • Hexane Extract: No significant.
		Plethysmometer and arthritis severity index	Progression of Arthritis (CIA Model)	Ethanol Extract: At 100 mg/kg, partial recuperation observed (89.0 ± 12.0% at 24th day). At 300 mg/kg, significant ↓ in arthritis progression was observed (71.7 ± 15.8%; $p < 0.01$). Comparable to ketorolac and dexamethasone.
7	Palomino-Pacheco et al. (2024)	Acute toxicity studies	Toxicology	No toxic effects observed at 2000 mg/kg. No deaths or organ abnormalities noted in macroscopic and histopathological analyses

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No.	Author	Tools	Outcome	Result
		Biochemical and histopathological analysis	Biochemical profile	No significant alterations in AST, ALT, urea, creatinine or lipid profiles. No histopathological changes in organs across all doses
		Monosodium Urate (MSU)-Induced Arthritis Vernier calliper and histopathology	Oedema formation	Significant dose-dependent in ankle swelling: 8.17% at 500 mg/kg vs. 19.34% (control, $p < 0.001$). Reduced inflammatory infiltrates.
		Oxonate-Induced Hyperuricemia Biochemical analyser	Reduce uric acid	Significant reduction in serum uric acid levels: 3.20 mg/dL at 500 mg/kg (39.51% reduction, $p < 0.05$). Comparable to normal control group.
		Analgaesic Activity (Acetic Acid Writhing) Observation of writhing behavior	Pain	Dose-dependent inhibition of writhing: 83.66% at 500 mg/kg, comparable to tramadol (89.92%, $p < 0.001$).
8	Sailaja et al. (2022)	Griess reagent method	NO production	Significant dose-dependent ↓ in NO production: 65% reduction at 1 μM MIC-1 compared to Lipopolysaccarides-treated control ($p < 0.05$).
		RT-qPCR	Pro-inflammatory gene expression	MIC-1 (1 μM) significantly ↓ TNF-α, IL-1β, IL-6, and Ifn-α gene expression levels by 60-80% in LPS-stimulated myoblasts
		Immunofluorescence microscopy	NF-κB nuclear translocation	MIC-1 (1 μM) nuclear NF-κB translocation by 70% compared to LPS-treated cells ($p < 0.05$).
		RNA sequencing	Transcriptomic changes in myoblasts	MIC-1 repressed 1,104 genes upregulated by LPS, including pathways related to innate immunity and inflammation.
		RT-qPCR	Cytokine expression in skeletal muscle	Daily oral MIC-1 (80 mg/kg) ↓ TNF-α, IL-1β, IL-6, and Ifn-α gene expression by 50-75% in LPS-treated mice ($p < 0.05$).
		RNA sequencing	Global transcriptomic changes in muscle	MIC-1 downregulated 952 genes induced by LPS, with pathways involving the immune system and inflammation being significantly suppressed.

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No.	Author	Tools	Outcome	Result
9.	Saleem et al. (2020)	• Digital Vernier Caliper • Plethysmometer	Inflammatory reaction - oedema	↓ oedema between treatment group – received 3 different extracts of Ifn-α at dosage of 600 mg/kg and piroxicam (anti-inflammatory drug) • 82.28% inhibition of methanolic extract • 80.3% inhibition of aqueous extract • 77.75% inhibition of piroxicam • 67.79% inhibition of ethyl acetate extract Between NC, ADC and treatment group • NC showed no signs of edema • ADC group exhibited significant paw swelling. • The treatment groups receiving *Moringa oleifera* extracts showed marked improvement in paw edema compared to the ADC group
		Weighing scale	Reduce body weight	↓ weight in ADC group compared to NC group Slowed down reduction of body weight between treatment group (methanolic and aqueous extract) at doses of 600 mg/kg compared to NC and piroxicam
		HRBC membrane stabilisation assay	Hematological parameter	Between treatment group and ADC group: • Normalised RBC counts and Hb levels in *Moringa oleifera* extracts or piroxicam
10.	Shamlan et al. (2021)	Custom multiplex immunoassay based on LuminexTM xMapTM	Anti-inflammatory markers	↑ anti-inflammatory cytokines (IL-4, IL-13, and IL-10) ($p < 0.05$) in all treatment groups (ML, MO, and MLO groups) compared with those in the Arth group.
			Proinflammatory markers	• ↑ proinflammatory cytokines (IL-6, IL-1b, and TNF-α) ($p < 0.05$) in the Arth group compared to the control group. • IL-6 level in all treatment groups ($p < 0.05$), but the lowest level was observed in the MO group, followed by the MLO group and then the ML group. • IL-1b level with the lowest level in the MLO group, followed by the MO group and then the ML group. • ↑ TNF-α level with the lowest level in the MO, followed by the MLO and ML groups

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No.	Author	Tools	Outcome	Result
11.	Tamrat et al. (2017)	Tail flick test	Pain	Chloroform Fraction: • 400 mg/kg dose of CF demonstrated significant analgesic activity compared to the negative control (tweet 80) at 90 minutes with protection 41.2% protection, $p < 0.01$. • But significantly lower compared to the positive control morphine (20 mg/kg), which achieved 90.3% protection at 90 minutes. Methanol Fraction: • All doses of MF (100, 200, 400 mg/kg) showed statistically significant increases in tail-flick latency compared to the negative control (tweet 80) ($p < 0.001$). • The 400 mg/kg dose of MF provided the highest effect with 46.6% protection at 90 minutes, but lower than positive control morphine (90.3% protection). Aqueous Fraction: • All doses of AF (100, 200, 400 mg/kg) exhibited highly significant analgesic activity compared to the negative control ($p < 0.001$). • 400 mg/kg dose of AF produced the highest protection of 73.6% at 120 minutes, compared to positive control morphine (62.1% at 120 minutes).
		Writhing test	Reduce Pain	Chloroform Fraction: • Significant inhibition was observed only at the 400 mg/kg dose (14.9% inhibition, $p < 0.01$), but this was far less than the positive control aspirin (150 mg/kg) (50.4% inhibition). Methanol Fraction: • All doses of MF (100, 200, 400 mg/kg) significantly reduced writhing compared to the negative control ($p < 0.001$). • 400 mg/kg dose showed 53.5% inhibition, compared to positive control aspirin (50.4%). Aqueous Fraction: • All doses of AF (100, 200, 400 mg/kg) demonstrated significant analgaesic effects compared to the negative control ($p < 0.001$). • The 400 mg/kg dose produced the highest writhing inhibition of 58.0%, compared to positive control aspirin (48.8%).

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No.	Author	Tools	Outcome	Result
		Carrageenan-Induced Paw Edema	Inflammatory reaction - edema	Chloroform Fraction: • 400 mg/kg dose of CF showed significant inhibition of paw oedema compared to the negative control (tweet 80) ($p < 0.05$). • The maximum inhibition was 24.4% at 2 hours, significantly lower than positive control aspirin (63.9% at 2 hours, $p < 0.001$). Methanol Fraction: • All doses of MF (100, 200, 400 mg/kg) significantly reduced paw oedema volume compared to the negative control starting from the 2nd hour ($p < 0.001$). • The 400 mg/kg dose of MF showed 52.2% inhibition at 2 hours, lower than positive control aspirin (63.9% at 2 hours). Aqueous Fraction: • All doses of AF (100, 200, 400 mg/kg) exhibited significant anti-inflammatory activity compared to the negative control (distilled water) ($p < 0.001$). • The 400 mg/kg dose of AF provided 67.0% inhibition at 2 hours compared to positive control aspirin (62.8% at 2 hours).

Arth: Arthritic rats (control positive) administered with standard diet; ML: Arthritic rats administered with 0.5 g of dried moringa leaves + standard diet; MO: Arthritic rats administered with 1 ml of Moringa oil + standard diet; MLO: Arthritic rats administered with (0.5 g of dried moringa leaves + 1 ml of Moringa oil) + standard diet

ADC: Arthritic control group; AF: Aqueous fraction; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase ; CAT: Catalase; CF: Chloroform fraction; CRP: C-reactive protein; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ELISA: Enzyme-linked immunosorbent assay; ESR: Erythrocyte sedimentation rate; FI: Functional index; H&E: Hematoxylin and eosin; Hb: Hemoglobin; Ifn-α: Interferon-alpha; IL: Interleukin; HRBC: Human red blood cell Interleukin; LPS: Lipopolysaccharide; MDA: Talondialdehyde; MF: Methanol fraction; MIC-1: Moringa isothiocyanate-1; MO: *Moringa oleifera*; NC: Normal control group; NO: Nitric oxide; RBC: Red blood cell; RNA: Ribonucleic acid; RT-qPCR: Reverse transcription quantitative polymerase chain reaction; SOD: Superoxide dismutase; TLCs: Total leukocyte counts; TNF-α: Tumor necrosis factor-alpha; mg: milligram; kg: kilogram; g: Gram; mL: millilitre; µM = micromolar; h: hour

near-normal values. Higher doses (500 mg/kg) also showed improvement, although slightly less effective compared to the lower dose (Mahdi et al. 2018). The study also found that ESR levels improved significantly in all treatment groups, including 250 and 500 mg/kg doses of moringa extract and indomethacin (Mahdi et al. 2018). Additionally, Saleem et al. (2020) stated that treatment with methanolic and aqueous extracts of moringa at 600 mg/kg normalised RBC counts and Hb levels in arthritic rats, similar to the standard drug piroxicam.

(iii) Antioxidant effect

Studies highlighted the potent antioxidant activity of *Moringa* species. Adedapo et al. (2015) demonstrated concentration-dependent antioxidant properties through 2,2-diphenyl-1-picrylhydrazyl assays. The scavenging activity increased with the dose, achieving the highest antioxidant effect at 20 mg/mL (Adedapo et al. 2015). Mahajan et al. (2007) reported significant reductions in oxidative stress markers, such as malondialdehyde (MDA) and improvements in antioxidant enzyme activity, including superoxide dismutase (SOD) and catalase (CAT). These effects were comparable to dexamethasone in treated groups, indicating the ability of moringa extracts to neutralise free radicals and mitigate oxidative damage (Mahajan et al. 2007).

Palomino-Pacheco et al. (2024) reported that moringa extract at 500 mg/kg demonstrated strong antioxidant activity, significantly reducing serum uric acid levels in hyperuricaemic models by 39.51%.

Observing the effect of moringa at the molecular level, Sailaja et al. (2022) reported that transcriptomic analyses showed that MIC-1 downregulated pathways related to oxidative stress and innate immunity in muscle tissue. This indicated that moringa not only reduced inflammation but also alleviated oxidative stress at the molecular level (Sailaja et al. 2022).

(iv) Effect on body weight

Moringa extracts exhibited notable effects on body weight, often reflecting improved systemic health. Kumar et al. (2013) reported a significant increase in body weight across treatment groups receiving moringa extracts at doses of 125, 250 and 500 mg/kg. The increase ranged from +15 to +24.2 g and was comparable to the aspirin-treated groups, while the arthritic control groups showed significant weight loss (–28.4 g) (Kumar et al. 2013). Mahajan et al. (2007) noted that body weight reductions were significantly lower in moringa-treated groups compared to the diseased controls. This suggested that moringa may mitigate the catabolic effects commonly associated with chronic inflammation (Mahajan et al. 2007). Mahdi et al. (2018) observed a dose-dependent effect, with the 250 mg/kg dose significantly increasing body weight, while the 500 mg/kg dose did not show a significant difference compared to controls.

(v) Toxicology findings

Moringa extracts were found to be safe within the tested limits. Adedapo et al. (2015) identified a safe dose of moringa extracts up to 800 mg/kg in acute toxicity studies. No adverse effects were observed below this threshold; although higher doses caused lethargy and some mortality (Adedapo et al. 2015). Fatima and Fatima (2016) and Kumar et al. (2013) extended the safety margin to 2000 mg/kg, with no observed toxic effects at these doses, confirming moringa's broad therapeutic safety profile.

Comparison of Main Findings between Human and Animal Studies

The findings across animal and human studies about the effectiveness of *Moringa* spp. for MSDs revealed notable similarities and differences in the outcomes for various themes (Table 6). Both animal and human studies demonstrated

TABLE 6 : Comparison between human and animal studies

No	Theme	Studies	
		Animal	**Human**
1.	Pain	↓ pain - Adedapo et al. 2015; Palomino-Pacheco et al. 2024; Tamrat et al. 2017	↓ pain - Abe et al. 2023; Celetaria et al. 2017; Shimizu et al. 2019; Singh et al. 2011
2.	Inflammatory markers	↓ CRP - Fatima & Fatima 2016 ↓ cytokine, IL, TNF - Mahajan et al. 2007; Shamlan et al. 2021 ↓ ESR - Mahajan et al. 2007; Mahdi et al. 2018 ↓ Uric acid - Palomino-Pacheco et al. 2024; Sailaja et al. 2022	↓ SAA and ESR level - Nugroho et al. 2023
	Inflammatory reaction	↓ edema - Adedapo et al. 2015; Fatima & Fatima 2016; Mahajan et al. 2007; Mahdi et al. 2018; Saleem et al. 2020; Tamrat et al. 2017; Kumar et al. 2013	X
3	Arthritis score	↓ score - Fatima & Fatima 2016; Mahajan et al. 2007; Mahdi et al. 2018; Martínez-González et al. 2017; Kumar et al. 2013	X
4	Anti-oxidant properties	Adedapo et al. 2015; Mahajan et al. 2007	X
5	Histopathological changes	Fatima & Fatima 2016	X
6	Body weight	↓ BW - Mahajan et al. 2007; Kumar et al. 2013 ↑ BW - Mahdi et al. 2018	X
7	RBC, Hb, Anemia - blood	↑ RBC, Hb - Mahdi et al. 2018; Kumar et al. 2013	X
8	Toxicological assessement	Safe under certain dosages - Adedapo et al. 2015; Fatima & Fatima 2016; Palomino-Pacheco et al. 2024	X
9	Mood	X	Improved mood but no significant difference - Abe et al. 2023

BW: Body weight; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; h: hour; IL: Interleukin; kg: kilogram; MDA: Malondialdehyde; mg: milligram; MO: *Moringa oleifera*; NSAID: Non-steroidal anti-inflammatory drug; RBC: Red blood cell; SAA: Serum amyloid A; TNF-α: Tumor necrosis factor-alpha; X: Not investigated

the ability of the tested interventions to reduce inflammatory activity and pain. Inflammatory markers such as ESR, CRP, IL and TNF were reduced in both models (Fatima & Fatima 2016; Mahajan et al. 2007; Mahdi et al. 2018; Nugroho et al. 2023; Palomino-Pacheco et al. 2024; Sailaja et al. 2022; Shamlan et al. 2021). Likewise, the severity of pain was also reduced (Abe et al. 2023; Adedapo et al. 2015; Celetaria et al. 2017; Shimizu et al. 2019; Singh et al. 2011; Tamrat et al. 2017).

Conversely, notable differences were observed in the outcomes related to weight in animal studies. Animal studies exhibited varied effects on body weight, with interventions reducing or increasing weight depending on the context (Mahdi et al. 2018; Kumar et al. 2013), whereas no data on body weight were available

for humans. However, mood improvements were only observed in human studies, where interventions led to better but statistically insignificant differences in emotional outcomes (Abe et al. 2023). This suggested potential psychosocial benefits unique to human subjects that were harder to model in animal studies.

Toxicological assessments were conducted primarily in animal studies. It demonstrated safety under certain dosages, which highlighted an area for further exploration in human models (Adedapo et al. 2015; Palomino-Pacheco et al. 2024). Other assessments done only in animal studies were inflammatory reaction, specifically in reducing oedema/swelling (Adedapo et al. 2015; Fatima & Fatima 2016; Mahajan et al. 2007; Mahdi et al. 2018; Saleem et al. 2020; Tamrat et al. 2017; Kumar et al. 2013), arthritis score or symptoms (Fatima & Fatima 2016; Mahajan et al. 2007; Mahdi et al. 2018; Martínez-González et al. 2017; Kumar et al. 2013), antioxidant properties (Adedapo et al. 2015; Mahajan et al. 2007), histopathological changes (Fatima & Fatima 2016) and haematological properties, which included RBCs and Hbs (Mahdi et al. 2018; Kumar et al. 2013). Figure 2 summarised the comparison between animal and human studies.

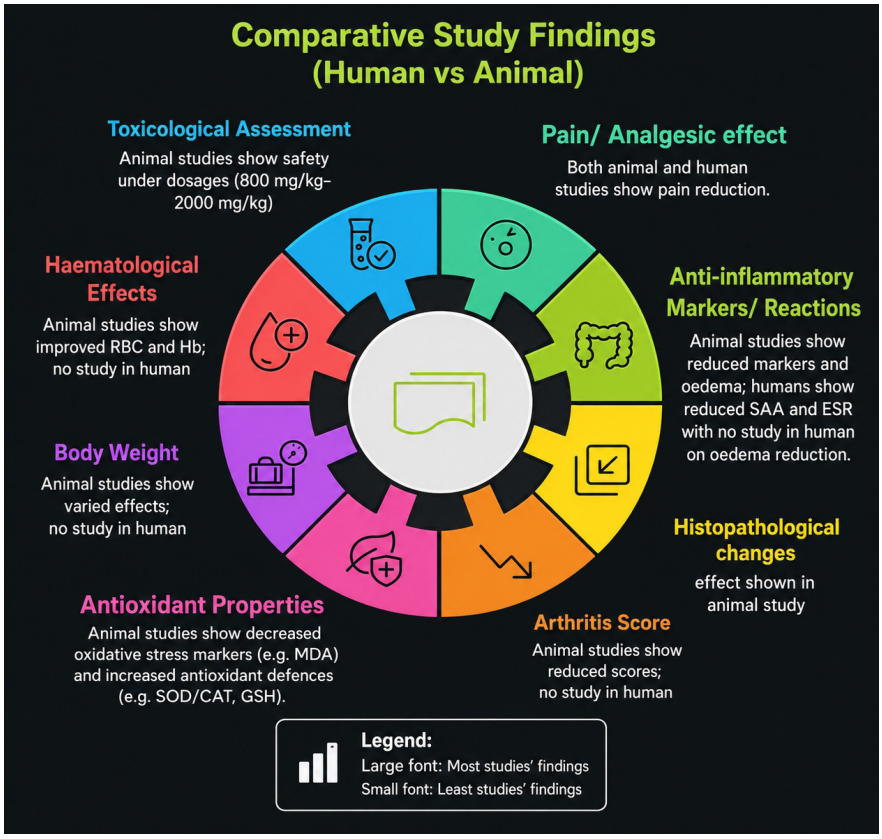

FIGURE 2: Comparison of animal and human study findings on the effects of *Moringa* sp. in musculosketal disorder; RBC: Red blood cell; Hb: Hemoglobin; SAA: Serum amyloid A; ESR: Erythrocyte sedimentation rate; mg: miligram; kg: kilogram. *Drawn using Canva (Canva Pty Ltd., Sydney, Australia)*

DISCUSSION

Overview of Findings

This systematic review highlights that the therapeutic effects of *Moringa* species correspond strongly with key stages of the OA pathogenesis cascade. OA typically progresses from mechanical overload, causing cartilage degradation, followed by synovial inflammation, matrix metalloproteinase (MMP) activation and finally a self-perpetuating degenerative cycle. The findings from human and animal studies show that moringa may intervene at multiple points in this cascade, suggesting possible disease-modifying potential rather than acting solely as a symptomatic agent.

Across the included studies, moringa also consistently demonstrated significant anti-inflammatory, analgesic and antioxidant properties. Preclinical data further support its role in cartilage protection, antioxidant defence, and bone formation (Liu et al. 2022a; Parihar et al. 2022). Furthermore, toxicity studies also indicate a wide safety margin, with no major adverse effects at doses up to 2000 mg/kg in animal models.

How Moringa Disrupts the Osteoarthritis Pathogenesis Cascade

(i) Mechanical overload induced oxidative stress and cartilage degradation

Mechanical overload of the joint leads to elevated oxidative stress in chondrocytes, impairing extracellular matrix (ECM) turnover (Du et al. 2025). In view of this long-standing insult, Meles et al. (2025) demonstrated moringa's potent antioxidant activity, with evidence of reduced MDA and increased SOD and catalase. These antioxidant effects suggest that moringa may protect chondrocytes from oxidative injury, thus slowing early cartilage degradation (Bagus Gede et al. 2025), especially among overweight or obese individuals who experience higher mechanical and oxidative loading. This is also primarily attributed to its rich content of flavonoid and phenolic compounds, which facilitate the scavenging of reactive oxygen species (ROS) and suppression of lipid peroxidation. The antioxidant potential of moringa compounds, including quercetin and chlorogenic acid is comparable or superior to conventional antioxidants such as vitamins C and E (Alam et al. 2021).

(ii) Cartilage damage induced synovial inflammation

Cartilage damage releases matrix fragments that stimulate synovial macrophages and fibroblasts, increasing cytokines such as TNF-α, IL-1β and IL-6 (Liu et al. 2022b). This review found consistent and significant reductions in these cytokines across both human and animal trials. Furthermore, animal studies consistently report reductions in inflammatory markers, such as CRP, IL-6, TNF-α and SAA, supporting its role as a systemic anti-inflammatory agent (Fatima & Fatima 2016; Mahajan et al. 2007; Mahdi Hj et al. 2018; Palomino-Pacheco et al. 2024; Sailaja et al. 2022; Shamlan et al. 2021). These mechanistic pathways consistently provide a strong biological foundation for the symptomatic improvements observed in humans. The anti-inflammatory efficacy of moringa has been also widely studied in animals using carrageenan-induced paw oedema models, which mimic acute inflammation via histamine, serotonin and prostaglandin-mediated pathways (Adedapo et al. 2015; Fatima & Fatima 2016; Mahajan et al. 2007; Martínez-González et al. 2017; Palomino-Pacheco et al. 2024; Saleem et al. 2020; Tamrat et al. 2017). Moringa effectively inhibits COX enzymes and reduces PGE2 synthesis (Dzoyem et al. 2017; Patil et al. 2019). Its antioxidant properties provide an additional protective mechanism by preventing oxidative tissue damage, which contributes to chronic inflammation (Saleem et al. 2020; Shahbaz et al. 2024). These findings suggest that moringa may limit the progression from cartilage injury to synovial inflammation, an important early turning point in OA progression. Reductions in ESR, CRP and SAA further strengthen moringa's role in inhibiting synovial inflammatory activation

(Nugroho et al. 2023).

(iii) Synovial inflammation driven activation of matrix metalloproteinases

Synovial inflammation drives the overexpression of metalloproteinases (MMPs) (e.g., MMP 1, MMP 3, MMP 13), accelerating cartilage breakdown (Sanchez-Lopez et al. 2022). Although the included studies did not directly quantify MMP levels, the observed suppression of TNF-α and IL 1β, which are major upstream regulators of MMP expression, strongly implies that moringa may indirectly inhibit MMP-mediated catabolic activity (Xie et al. 2020). The significant reduction of oxidative stress markers such as 8-OHdG in human trials further confirms moringa's protective effects at the cellular level (Abdel-Daim et al. 2020; Abdul Hisam et al. 2018; Abe et al. 2023; Sadek et al. 2017). These findings suggest that moringa could be a valuable adjunct in therapeutic approaches targeting oxidative and inflammatory pathophysiology prevalent in MSDs. However, while promising, the long-term clinical benefits remain to be fully elucidated. Future research should prioritise clinical studies, while focusing on MSDs, and must include the pharmacokinetics and pharmacodynamic analyses across diverse populations in order to establish standardised dosage recommendations and optimise therapeutic precision. Moreover, improvements in histopathological indicators in animal models also align with reduced enzymatic cartilage destruction (Fatima & Fatima 2016).

(iv) Matrix metalloproteinases mediated cartilage destruction and the vicious cycle of osteoarthritis

OA progression accelerates through a vicious cycle of oxidative stress, inflammation and cartilage loss. Moringa appears to disrupt this cycle through several coordinated biological actions. First, its antioxidant effects help neutralise reactive oxygen species and protect cartilage from oxidative degradation (Bagus Gede et al. 2025). It also exhibits anti-inflammatory activity that suppresses cytokines responsible for chronic synovitis and MMP activation (Sanchez-Lopez et al. 2022). In addition, moringa provides analgesic effects, which may help reduce maladaptive compensatory loading that arises from pain (Adedapo et al. 2015; Mahdi et al. 2018; Martínez-González et al. 2017; Palomino-Pacheco et al. 2024; Tamrat et al. 2017). Animal study further indicate osteogenic and chondroprotective actions, including enhanced extracellular matrix synthesis and improved bone remodelling (Fatima & Fatima 2016). Taken together, these mechanisms suggest that moringa acts at multiple key nodes of the OA cascade and may serve as a multi-targeted adjunct for managing degenerative MSDs.

Other Benefits from Human Studies

(i) Analgesic effect

Human studies suggest that moringa possesses promising analgesic and anti-inflammatory effects for musculoskeletal pain, particularly in arthritic conditions. Its pain-relieving properties are attributed to mechanisms such as the inhibition of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and the suppression of the cyclooxygenase (COX) pathway, which mediates prostaglandin-induced pain and inflammation (Adedapo et al. 2015; Mahdi et al. 2018; Martínez-González et al. 2017; Palomino-Pacheco et al. 2024; Tamrat et al. 2017). Furthermore, moringa appears to modulate pain through multiple mechanisms, including peripheral and central antinociceptive pathways (Sulaiman et al. 2009).

However, these clinical trials have several limitations, whereby it was conducted in short intervention durations, comprised variable product formulations (seed extracts, leaf products, oil) and lacked comparative trials to NSAIDs or established analgesics. While some comparative studies hint at analgesic effects similar to conventional NSAIDS like aspirin (Patnaik et al. 2018), the current body of human evidence is not as robust as preclinical data supporting this. Therefore, further clinical trials are imperative to definitively establish moringa's

comparative efficacy and optimal application in human pain management.

(ii) Lipid metabolism modulation

Beyond its anti-inflammatory and analgesic effects, moringa demonstrates multi-mechanistic benefits for musculoskeletal health. It modulates lipid metabolism, reducing total cholesterol (TC), low-density lipoprotein (LDL-C) and triglycerides while increasing high-density lipoprotein (HDL) levels (Blyth et al. 2019). This lipid-lowering effect indirectly mitigates joint stress and systemic inflammation, which are often comorbidities with MSDs.

(iii) Bone mineralisation

Furthermore, moringa's rich nutritional profile, including high levels of calcium, phosphorus and Vitamin K, directly supports bone mineralisation and may enhance chondrocyte activity and extracellular matrix synthesis, thereby supporting cartilage regeneration and bone formation (Abd Rani et al. 2018; Hartvigsen et al. 2018).

This suggests a potential role for moringa in maintaining bone density, particularly benefiting older populations vulnerable to poor mineralisation. Its antioxidant and anti-inflammatory properties contribute to improved erythropoiesis, with studies reporting increases in RBC count and haemoglobin levels, likely due to its rich iron, folate and vitamin B12 content (Divya et al. 2024). These benefits position moringa as a strong candidate for further clinical trials as a nutritional supplement for high-risk populations, such as those with OA or malnutrition.

(iv) Sleep quality enhancement

Emerging evidence also suggests that moringa may enhance sleep quality, an important factor in musculoskeletal recovery and overall well-being. Bioactive compounds such as oleic acid and stigmasterol modulate serotonin and gamma-aminobutyric acid (GABA) pathways, promoting relaxation and reducing anxiety-related sleep disturbances (Liu et al. 2022c). These neuromodulator effects highlight moringa's potential applications in managing sleep disorders commonly associated with chronic pain and inflammation. However, heterogeneity across study protocols has limited the comparability with the clinically relevant improvement in mood and sleep, as the findings were marginal. Therefore, to validate these secondary advantages, larger and well-powered clinical trials are required.

Other Benefits from Animal Studies

(i) Inconclusive effect on body weight

The effects of moringa extracts on body weight in animal models are inconsistent. For instance, Mahajan et al. (2007) reported weight loss, while Kumar et al. (2013) observed a significant increase in body weight. Meanwhile, Mahdi et al. (2018) highlighted a dose-dependent response, where moderate doses increased body weight but higher doses showed no significant effect. These findings reflect a complex interplay between inflammation, metabolic regulation and dosing. Chronic inflammation in arthritic models promotes catabolic loss of muscle and fat, which can be mitigated by moringa's bioactive compounds, including phenolics, flavonoids and isothiocyanates through anti-inflammatory and antioxidant actions that restore nutrient utilisation and support tissue maintenance (Mukherjee et al. 2024). Variations in response, including weight gain at moderate doses and lack of effect at higher doses, may result from saturation of metabolic pathways or biphasic pharmacodynamics (Calabrese 2013). These observations suggest that moringa has the potential to preserve body weight and metabolic stability under inflammatory conditions. However, the effects are highly dose- and context-dependent, emphasising the need for standardised dosing and further studies to guide clinical translation.

(ii) Toxicology and safety

Animal studies indicate that moringa extracts

are generally well tolerated, with a wide safety margin that supports their potential therapeutic use (Fatima & Fatima 2016; Kumar et al. 2013). The absence of adverse effects at doses up to 2000 mg/kg suggests that its bioactive compounds, including phenolics, flavonoids and isothiocyanates exert protective antioxidant and cytoprotective actions on vital organs (Chiș et al. 2023), which may mitigate toxicity even at relatively high intake. Occasional lethargy and mortality at supra-therapeutic doses highlight the importance of dose optimisation, as excessive concentrations may overwhelm metabolic or detoxification pathways. Collectively, these findings underscore moringa's favourable safety profile and support its consideration as a functional food or adjunct therapy, while also emphasising the need for long-term and human studies to confirm optimal dosing and chronic safety.

Limitation

Despite its benefits, this review found limited studies systematically assessing the side effects of moringa. Many studies focus primarily on its therapeutic effects, with limited safety data. In addition, the number of high-quality human clinical trials remains limited, with most studies characterised by small sample sizes, short intervention durations and considerable methodological heterogeneity. Even though leaves are the most widely used and nutrient-dense part, the significance of selective sourcing is highlighted by other plant parts, especially the roots and stems, which contain potentially dangerous alkaloids. Additionally, the processing methods have a significant impact on the stability of bioactive substances. For example, vacuum drying preserves phytochemical integrity better than traditional air drying. Therapeutic effects cannot be consistently compared across studies in the absence of defined extraction and processing processes, underscoring the necessity of standardised production procedures to guarantee repeatable clinical results. Besides, the absence of standardised preparation methods and dosage guidelines further complicates safety assessments or dose-response relationships, highlighting the need for future studies incorporating consistent protocols and adverse event monitoring.

Another important limitation relates to the potential for herb–drug interactions, particularly with medications commonly prescribed for MSDs. Moringa shares mechanistic pathways with NSAIDs, including partial COX-2 inhibition, which may theoretically potentiate gastrointestinal irritation or ulceration when co-administered. Similarly, its immunomodulatory and anti-inflammatory properties may augment the pharmacological activity of disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, potentially increasing the risk of hepatotoxicity or excessive immunosuppression. Although these interactions are biologically plausible, empirical evidence in humans is sparse, underscoring the need for dedicated interaction studies before moringa can be safely integrated into routine clinical management of musculoskeletal diseases.

Moreover, dose-dependent efficacy has been observed in animal studies within this systematic review, with limitations remaining in translating these findings to clinical practice due to species-specific metabolic differences and reliance on subjective pain assessments in human studies. Lastly, the absence of pharmacokinetic and pharmacodynamic data in this review hinders the development of standardised clinical dosing guidelines.

Perspective and Future Research Priorities

Although moringa presents a promising adjunctive therapy for MSDs, several gaps remain in translating these effects into long-term clinical benefits. Current evidence, particularly from human studies, is limited in scope and quality, highlighting the need for well-designed, large-scale clinical trials. Randomised controlled trials with double-blind, placebo-controlled designs should evaluate standardised moringa extracts, focusing on adult populations with OA or other relevant MSDs. These studies should assess key

outcomes such as pain reduction, functional improvement, inflammatory biomarkers and cartilage preservation. Dose-ranging studies are essential to establish optimal therapeutic concentrations, while pharmacokinetics, long-term safety and potential interactions with conventional medications, particularly NSAIDs and DMARDs, require thorough investigation.

Furthermore, optimising preparation and extraction methods will enhance consistency and efficacy in therapeutic applications. Given the global burden of MSDs and the growing interest in natural treatment alternatives, Moringa holds potential as a complementary or adjunctive therapy. High-quality studies addressing these gaps will be critical to inform clinical guidelines, ensure both efficacy and safety, and enhance the integration of moringa into long-term musculoskeletal health management.

CONCLUSION

This systematic review highlights the therapeutic potential of *Moringa* species in the management of MSDs, demonstrating significant anti-inflammatory, analgesic and antioxidant properties. Evidence from both preclinical and clinical studies suggests that Moringa effectively reduces pain, inflammation and oxidative stress while supporting cartilage and bone regeneration. Its bioactive compounds, including flavonoids, polyphenols and essential minerals contribute to its multifaceted benefits in musculoskeletal health.

Additionally, its high safety profile, with no major adverse effects reported at recommended doses, underscores its potential as a natural therapeutic option. Nevertheless, the clinical evidence remains preliminary, and the translation of preclinical efficacy to long-term human therapeutic benefit has yet to be fully established. Strengthening the evidence base will require well-designed, larger clinical trials incorporating standardised moringa extracts, objective biomarkers, dose optimisation and comprehensive safety monitoring. This rigorous validation will enhance the scientific evidence of moringa as a natural adjunctive therapy for enhancing musculoskeletal health and potentially reducing reliance on long-term pharmacotherapy.

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TABLE S1: Charting Form

Item	Variable definition	Description of data extraction/ comment
	Human study	
Author	The writer of the article	
Year	Year of publication	
Nation and location	Name of country and location where the study done	
Study design	Type of research design used	
Sample population	Subset of the target population from which the sample is selected	
Sample size	Number of respondents	
Goal	Objective of the study	
Type and dosage of moringa	Species and dose use	
Laboratory analysis	Tools used	
Sampling procedure for outcome measured	Sampling method Intervention or control group	
Primary finding	Categorised into: - Pain -Inflammatory markers - Inflammatory reaction - Arthritis score - Anti-oxidant properties - Histopathological changes - Body weight (BW) - Hematological changes - Toxicological assessment - Mood	
Primary statistical analyses	Value recorded for each finding	
	Animal study	
Author	The writer of the article	
Year	Year of publication	
Nation and location	Name of country and location where the study done	
Study design	Type of research design used	
Sample population	Subset of the target population from which the sample is selected	
Sample size	Number of respondents	
Goal	Objective of the study	
Type and dosage of moringa	Species and dose use	
Duration of the experiment	Time frame	
Laboratory analysis	Tools used	
Sampling procedure for outcome measured	Sampling method Intervention or control group	
Primary finding	Categorised into: Pain Inflammatory markers Inflammatory reaction Arthritis score Anti-oxidant properties Histopathological changes Body weight (BW) Hematological changes Toxicological assessment Mood	
Primary statistical analyses	Value recorded for each finding	