

Cardioprotective and immunomodulatory mechanisms of *Moringa oleifera*: A critical review of phytochemical evidence, clinical gaps, and future research priorities

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Abstract

Cardiovascular diseases (CVDs) and immune-related disorders are major sources of morbidity and mortality worldwide, with chronic inflammation as a predominant pathophysiologic factor. *Moringa oleifera* Lam., rich in nutrients and possessing numerous pharmacological properties, has attracted attention as a potential adjunct to treatment strategies. This critical review evaluates the cardioprotective and immunomodulatory mechanisms of *M. oleifera*, moving beyond nutritional composition to examine the molecular pathways involved, identify gaps in clinical evidence, and propose future research priorities. A literature search was conducted in PubMed, Scopus, Web of Science, and ScienceDirect, focusing on publications from 2015 to 2025, and included preclinical studies, clinical trials, systematic reviews, and meta-analyses, which were critically appraised for methodological rigor and evidence certainty. Preclinical evidence indicates that *M. oleifera* exerts cardioprotective and immunomodulatory activities through mechanisms including NF- κ B inhibition, Nrf2/Keap1 activation, PI3K/Akt modulation, and PPAR- γ activation. Bioactive compounds, particularly flavonoids (quercetin, kaempferol), isothiocyanates (moringin), and polysaccharides (arabinogalactans), suppress pro-inflammatory cytokines (TNF- α , IL-1 β), inhibit pro-inflammatory enzymes (iNOS, COX-2), reduce the prostaglandin PGE₂, promote anti-inflammatory cytokines (IL-10), and enhance immune cell function, including CD4⁺/CD8⁺ T-lymphocyte proliferation and NK-cell cytotoxicity. However, clinical translation remains limited. Meta-analyses demonstrate very low certainty of evidence for cardiometabolic outcomes, with no significant effects on most parameters and only a modest, non-robust reduction in diastolic blood pressure. In contrast, more consistent positive evidence exists for immune function, particularly in populations living with HIV. Although preclinical potential is substantial, clinical translation has not kept pace. Current evidence does not support consistent cardiometabolic benefits of *M. oleifera* supplementation in adults. Future research should prioritize high-quality randomized controlled trials with standardized preparations, nanotechnology-enabled bioavailability enhancement, biomarker-driven mechanistic validation, robust quality control, long-term safety monitoring, and systems biology approaches to bridge the gap between preclinical evidence and clinical application.

Keywords: *Moringa oleifera*, cardioprotection, immunomodulation, phytochemicals, clinical translation.

Mecanismos cardioprotetores e imunomoduladores de *Moringa oleifera*: Uma revisão crítica das evidências fitoquímicas, lacunas clínicas e prioridades para pesquisas futuras

Resumo

As doenças cardiovasculares (DCVs) e os distúrbios imunológicos representam as principais causas de morbidade e mortalidade em nível mundial, tendo a inflamação crônica como um fator fisiopatológico predominante. *Moringa oleifera* Lam., rica em nutrientes e dotada de diversas propriedades farmacológicas, tem atraído atenção

como um potencial adjuvante para estratégias terapêuticas. Esta revisão crítica avalia os mecanismos cardioprotetores e imunomoduladores de *M. oleifera*, indo além da composição nutricional para examinar as vias moleculares envolvidas, identificar lacunas nas evidências clínicas e propor prioridades para pesquisas futuras. Foi realizada uma busca abrangente da literatura nas bases de dados PubMed, Scopus, Web of Science e ScienceDirect, com ênfase em publicações entre 2015 e 2025, incluindo estudos pré-clínicos, ensaios clínicos, revisões sistemáticas e metanálises, que foram avaliados criticamente quanto ao rigor metodológico e ao grau de certeza das evidências. Evidências pré-clínicas indicam que *M. oleifera* exerce atividades cardioprotetoras e imunomoduladoras por meio de mecanismos que incluem a inibição do NF- κ B, a ativação da via Nrf2/Keap1, a modulação da PI3K/Akt e a ativação do PPAR- γ . Compostos bioativos, especialmente flavonoides (quercetina e kaempferol), isotiocianatos (moringina) e polissacarídeos (arabinogalactanas), suprimem citocinas pró-inflamatórias (TNF- α e IL-1 β), inibem enzimas pró-inflamatórias (iNOS e COX-2), reduzem a prostaglandina PGE₂, promovem citocinas anti-inflamatórias (IL-10) e melhoram a função das células do sistema imunológico, incluindo a proliferação de linfócitos T CD4⁺/CD8⁺ e a atividade citotóxica das células NK. Entretanto, a tradução clínica permanece limitada. Metanálises demonstram um nível muito baixo de certeza das evidências para desfechos cardiometabólicos, sem efeitos significativos para a maioria dos parâmetros avaliados e com apenas uma redução modesta e não robusta da pressão arterial diastólica. Em contraste, existem evidências positivas mais consistentes para a função imunológica, particularmente em populações vivendo com HIV. Embora o potencial pré-clínico seja substancial, a tradução clínica não acompanhou esse avanço. As evidências atuais não sustentam benefícios cardiometabólicos consistentes da suplementação de *M. oleifera* em adultos. Pesquisas futuras devem priorizar ensaios clínicos randomizados de alta qualidade com preparações padronizadas, aumento da biodisponibilidade por nanotecnologia, validação mecanística baseada em biomarcadores, controle de qualidade robusto, monitoramento de segurança a longo prazo e abordagens de biologia de sistemas para reduzir a lacuna entre as evidências pré-clínicas e a aplicação clínica.

Palavras-chave: *Moringa oleifera*, cardioproteção, imunomodulação, fitoquímicos, tradução clínica.

1. Introduction

1.1 Background and rationale

Cardiovascular diseases (CVDs) remain the leading cause of death and disability worldwide and constitute a major public health challenge, particularly in low- and middle-income countries. The Global Burden of Disease (GBD) 2023 analysis estimated 19.2 million CVD deaths (95% UI: 17.4–20.4 million) and 437 million disability-adjusted life years (DALYs) (95% UI: 401–465 million) globally in 2023. The number of CVD deaths increased from 13.1 million in 1990 to 19.2 million in 2023, while prevalent CVD cases increased from 311 million to 626 million over the same period. Approximately 79.6% of the global CVD burden was attributable to modifiable risk factors, with high systolic blood pressure, dietary risks, high low-density lipoprotein cholesterol, and air pollution identified among the leading contributors (Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators, 2025).

Hypertension represents one of the most important modifiable risk factors for CVD and is a major contributor to premature mortality. The World Health Organization (WHO) estimated that the number of adults with hypertension increased from approximately 650 million in 1990 to 1.3 billion in 2019, with nearly half of affected individuals unaware of their condition (WHO) (Gheorghe et al., 2018). More recently, the WHO estimated that approximately 1.4 billion adults aged 30–79 years had hypertension in 2024, corresponding to about one-third of the global population in this age group. Approximately two-thirds of affected adults live in low- and middle-income countries, while about 600 million people remain unaware of their condition and only approximately 320 million have controlled blood pressure (WHO, 2025). These figures demonstrate the persistent global gap in hypertension detection, treatment, and control.

The economic consequences of CVD and hypertension are also substantial. Cardiovascular diseases, including hypertension, were estimated to impose approximately US\$3.7 trillion in economic costs on low- and middle-income countries between 2011 and 2025, equivalent to approximately 2% of their combined gross domestic product (Gheorghe et al., 2018). The continuing increase in CVD burden is associated with population growth, population aging, and increasing exposure to metabolic and environmental risk factors. In particular, the contribution of high body mass index to CVD burden has increased substantially since 1990, reflecting the changing global metabolic risk profile (Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators, 2025).

The contemporary cardiovascular burden is particularly concerning in low- and middle-income countries, where premature mortality remains substantial. The American Heart Association reported a global age-adjusted CVD mortality rate of approximately 235.2 per 100,000 population compared with 224.3 per 100,000 in the United States, reflecting persistent inequalities in cardiovascular health (Martin et al., 2025). These disparities are influenced by differences in prevention, diagnosis, treatment, health-care access, socioeconomic conditions, and exposure to modifiable risk factors.

Concurrently, immune-mediated inflammatory diseases (IMIDs) comprise a heterogeneous group of chronic disorders characterized by dysregulated immune responses and persistent inflammation. Analysis of GBD 2021 data demonstrated substantial geographical and temporal variation in the burden of major IMIDs, with high-sociodemographic-index regions generally showing higher incidence but lower mortality, whereas lower-sociodemographic-index regions experienced comparatively lower recorded incidence but higher mortality (Luo, 2024). These differences may reflect variations in disease detection, diagnostic capacity, access to treatment, health-care infrastructure, and survival.

The relationship between CVD and immune dysregulation is increasingly recognized as an important component of cardiovascular pathophysiology. Chronic inflammation contributes to endothelial dysfunction, lipid accumulation, immune-cell activation, and atherosclerotic plaque development. Immunometabolic interactions involving macrophages, T cells, inflammatory mediators, and metabolic pathways can therefore contribute to the initiation and progression of atherosclerotic cardiovascular disease (Fleetwood et al., 2024). The convergence of inflammation, oxidative stress, dyslipidemia, insulin resistance, and vascular dysfunction provides a biological rationale for investigating interventions capable of simultaneously influencing several of these pathways.

Growing interest in complementary approaches to chronic disease management has also increased scientific attention toward medicinal plants and other natural products. Traditional medicine remains an important component of health care in many populations, and WHO has estimated that a substantial proportion of the global population uses traditional medicine (WHO, 2022). Nevertheless, widespread traditional use should not be equated with demonstrated clinical efficacy. Rigorous investigation of medicinal plants therefore remains necessary to establish their pharmacological mechanisms, therapeutic effectiveness, safety, appropriate dosage, phytochemical standardization, and potential interactions with conventional medicines.

Among medicinal plants receiving increasing scientific attention, *Moringa oleifera* Lam. (family Moringaceae) represents a particularly promising candidate (Chiş et al., 2024; Gharsallah et al., 2023). The plant is native to the Indian subcontinent and is now widely cultivated throughout tropical and subtropical regions. Its leaves, seeds, pods, bark, roots, and flowers contain nutrients and diverse bioactive compounds, including flavonoids, phenolic compounds, glucosinolates, and isothiocyanates (Abdelazim et al., 2024). These constituents have been investigated for antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic, cardioprotective, and immunomodulatory properties.

The potential cardiometabolic relevance of *M. oleifera* has been summarized in systematic reviews. Evidence suggests that *M. oleifera* may influence glucose and lipid metabolism, oxidative stress, inflammation, and vascular function. Proposed mechanisms include modulation of NF- κ B signaling, activation of antioxidant pathways involving Nrf2, attenuation of oxidative stress, and regulation of metabolic pathways associated with hypertension, obesity, diabetes, and dyslipidemia (Louisa et al., 2022). These mechanisms are particularly relevant because oxidative stress and chronic low-grade inflammation are interconnected with several major cardiovascular risk factors.

The immunomodulatory effects of *M. oleifera* are similarly important. Experimental studies indicate that extracts and phytochemical constituents of the plant may modulate inflammatory mediators, including tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), interleukin-1 beta (IL-1 β), NF- κ B, and interleukin-10 (IL-10). A recent umbrella review of systematic reviews reported generally favorable anti-inflammatory and antioxidant effects associated with *M. oleifera*, with proposed involvement of NF- κ B, Nrf2, and NLRP3-related pathways (da Silva Parente et al., 2025).

However, the available evidence remains predominantly preclinical, and substantial heterogeneity exists in extraction methods, plant parts, doses, phytochemical composition, experimental models, and study quality. Consequently, these findings should be interpreted as evidence of therapeutic potential rather than established clinical efficacy (da Silva Parente et al., 2025).

The potential significance of *M. oleifera* therefore lies in its ability to influence multiple biological pathways implicated in cardiovascular and immune-mediated inflammatory disorders. Its reported antioxidant, anti-inflammatory, lipid-modulating, glucose-regulating, and immunomodulatory activities provide a plausible

mechanistic basis for further investigation. However, translation from traditional use and experimental evidence to clinical application requires rigorous assessment of standardized preparations, dose-response relationships, pharmacokinetics, toxicity, drug interactions, and clinical effectiveness. Accordingly, systematic investigation of the phytochemical composition and biological activities of *M. oleifera* is warranted to clarify its potential as a complementary therapeutic candidate for cardiometabolic and immune-mediated inflammatory conditions.

1.2 Scope and objectives of the review

Despite the extensive body of research on *M. oleifera*, much of the existing literature has focused on its nutritional composition, with comparatively less attention devoted to a critical, mechanistic evaluation of its therapeutic effects beyond basic nutrition. The present review aims to consolidate and critically evaluate the existing evidence on the cardioprotective and immunomodulatory mechanisms of *M. oleifera*, with a deliberate emphasis on moving *beyond* nutritional composition to examine the molecular and cellular pathways that underlie its therapeutic effects.

Previous evidence syntheses have reported substantial preclinical support for the cardioprotective, antihypertensive, antidiabetic, antioxidant, and immunomodulatory potential of *M. oleifera*. In particular, Mehta et al. (2026) reviewed studies published between 2015 and 2025 and identified 89 *in vivo*, 24 *in vitro*, 8 clinical, and 6 nanoformulation studies investigating *M. oleifera* in relation to major cardiovascular conditions. Their review also showed that leaves accounted for approximately 78% of the investigated plant material, with aqueous and ethanolic extracts being the predominant preparations and flavonoids, glucosinolates, and isothiocyanates among the principal bioactive constituents (Mehta et al., 2026). Importantly, these numerical findings represent the evidence base synthesized by Mehta et al. (2026) and are not results of the present review. The reported cardioprotective effects were associated with modulation of several molecular pathways, including NF- κ B, Nrf2/Keap1, PI3K/Akt, PPAR, AMPK, and MAPK signaling (Mehta et al., 2026).

Complementary experimental evidence suggests that individual *M. oleifera* constituents may exert anti-inflammatory effects through inhibition of cyclooxygenase and lipoxygenase activity, modulation of NF- κ B-dependent cytokine signaling, and attenuation of oxidative stress. Flavonoids such as quercetin and kaempferol, together with glucosinolates and their derived isothiocyanates, have therefore been proposed as important contributors to the plant's biological activity (Alidadi et al., 2023; Mehta et al., 2026). Collectively, these findings provide a mechanistic foundation for further investigation, while also highlighting the need to distinguish previously synthesized evidence from the specific evidence identified and evaluated in the present review.

Specifically, this review seeks to: (1) synthesise the current understanding of the phytochemical constituents of *M. oleifera* that underpin its bioactivity; (2) elucidate the molecular signalling pathways through which *M. oleifera* exerts cardioprotective effects; (3) examine the cellular and molecular mechanisms by which *M. oleifera* modulates immune function, including cytokine regulation, immune cell proliferation, and gut microbiome interactions; (4) critically appraise the clinical evidence base, identifying methodological deficiencies and knowledge gaps that limit translational progress; and (5) propose future research priorities for translating phytochemical promise into evidence-based therapeutic applications. By adopting this comprehensive and critical approach, the review aims to provide a balanced assessment that acknowledges both the substantial preclinical promise and the considerable challenges that must be overcome to establish *M. oleifera* as a credible adjunctive therapeutic agent in cardiovascular and immune health.

2. Materials and Methods

2.1 Review design and reporting framework

This work is a critical narrative review, not a systematic review. It was designed to consolidate, appraise, and interpret the existing literature on the cardioprotective and immunomodulatory mechanisms of *Moringa oleifera*, with explicit attention to the gap between preclinical evidence and clinical translation. Because the review does not employ a formal, pre-registered, reproducible search protocol with dual independent screening and quantitative synthesis, it does not claim to conform to the PRISMA 2020 statement, and no systematic review registration was undertaken.

Instead, the review was structured according to the SANRA (Scale for the Assessment of Narrative Review Articles) criteria, which emphasise justification of the review's importance, explicit aims, description of the literature search, referencing of primary literature, appropriate reasoning, and presentation of relevant and appropri-

ate data. This distinction is stated here to avoid the implication that the present search strategy was systematic or exhaustive.

2.2 Information sources and search strategy

A comprehensive but non-systematic search of the peer-reviewed literature was conducted using PubMed, Scopus, Web of Science, and ScienceDirect. The search was performed independently by the authors and was last updated in September 2025; no date limits were applied to database indexing, although the synthesis prioritised publications from 2015 to 2025 to reflect the most recent evidence base.

The search strategy combined free-text keywords and Medical Subject Headings (MeSH) terms, including "*Moringa oleifera*," "cardioprotective," "immunomodulatory," "anti-inflammatory," "antioxidant," "phytochemicals," "flavonoids," "glucosinolates," "clinical trials," and "systematic review." Boolean operators (AND, OR) were used to refine queries. The full search strings used for each database are provided in Supplementary Table S1, and the search was not restricted by language or publication type at the retrieval stage.

2.3 Eligibility criteria and study selection

Records were considered eligible if they addressed the phytochemistry, pharmacokinetics, preclinical pharmacology, or clinical effects of *M. oleifera* in relation to cardiovascular or immune endpoints. Priority was given to *in vivo* and *in vitro* mechanistic studies, randomised controlled trials, systematic reviews, and meta-analyses published between 2015 and 2025. Studies were excluded if they concerned plant species other than *M. oleifera*, reported no cardiovascular or immunological outcome, or were limited to agronomic or food-technology aspects without pharmacological relevance.

Screening was performed by the two authors. Because this is a narrative rather than a systematic review, records were not screened in duplicate by independent reviewers, and inter-rater agreement was not calculated. Titles and abstracts were screened first, followed by full-text assessment of potentially relevant articles. The number of records identified, screened, and included was not tracked prospectively, and therefore a PRISMA-style flow diagram cannot be provided. This limitation is acknowledged explicitly, and readers should interpret the synthesis as an expert critical appraisal rather than a reproducible systematic search.

2.4 Data extraction and synthesis

Data extracted from included studies encompassed plant part and preparation, extraction solvent, dose and route of administration, model system, duration of intervention, outcomes assessed, and reported mechanisms. Findings were synthesised thematically according to (i) phytochemical composition and organ-specific distribution, (ii) bioavailability and pharmacokinetic considerations, (iii) cardioprotective mechanisms, (iv) immunomodulatory mechanisms, and (v) clinical evidence and translational barriers. Where available, effect estimates and certainty-of-evidence ratings from published meta-analyses were reported verbatim rather than recalculated.

2.5 Use of non-peer-reviewed sources

In addition to peer-reviewed literature, we consulted a limited number of authoritative non-peer-reviewed sources for regulatory, safety, and pharmacovigilance information not typically published in indexed journals. These include the World Health Organization Global report on hypertension (2023) and its 2025 update, the American Heart Association Heart Disease and Stroke Statistics (2025), the Drugs.com monograph for *Moringa*, the Pharmacist's Letter safety profile, and the Scilit scholarly database. These sources provide contextual epidemiological data, product safety information, and adverse-event reporting, and the text clearly identifies them as such. This use is consistent with the narrative design of the review but is acknowledged as a deviation from the peer-review-only standard that would apply to a systematic review; it is therefore disclosed here rather than presented as part of a systematic search.

2.6 Quality and certainty of evidence

For clinical outcomes, the certainty of evidence was not independently re-graded. Instead, the GRADE assessments reported by the source meta-analyses (notably Crisan et al., 2025) were cited directly, including their

judgements of very low certainty for cardiometabolic outcomes. Risk of bias in the underlying trials was likewise taken from the source reviews rather than reassessed de novo.

2.7 Limitations of the review methodology

The principal methodological limitations are the absence of a pre-registered protocol, the absence of duplicate independent screening, the lack of a prospectively recorded study-selection flow, and the deliberate inclusion of selected authoritative grey sources for safety and epidemiological context. These choices are consistent with a critical narrative review but preclude claims of systematic exhaustiveness. Accordingly, the present work should be regarded as an interpretive synthesis intended to identify mechanistic themes and translational gaps, rather than as a definitive systematic evidence map.

3. Results

3.1 Phytochemical landscape of *Moringa oleifera*: The molecular foundation of bioactivity

3.1.1 Major classes of bioactive compounds

The remarkable therapeutic potential of *M. oleifera* is rooted in its exceptionally diverse phytochemical repertoire, which encompasses flavonoids, polyphenols, glucosinolates, isothiocyanates, alkaloids, polysaccharides, essential vitamins, minerals, and numerous other specialized metabolites. This rich chemical architecture underpins the plant's multifaceted pharmacological activities, including antioxidant, anti-inflammatory, immunomodulatory, and cardioprotective effects (Alidadi et al., 2023; Attakpa et al., 2017; Pareek et al., 2024).

Flavonoids constitute one of the most abundant and pharmacologically significant classes of compounds in *M. oleifera*. High-performance liquid chromatography (HPLC) analyses have consistently identified quercetin, kaempferol, and rutin as the predominant flavonoids in leaf extracts (Alidadi et al., 2023). These flavonoids serve as primary drivers of the plant's antioxidant and anti-inflammatory activities, functioning through direct free radical scavenging, metal chelation, and modulation of redox-sensitive signalling pathways. Notably, quercetin and kaempferol have been shown to inhibit pro-inflammatory enzymes, including cyclooxygenase and lipoxygenase, thereby attenuating the production of inflammatory mediators (Alidadi et al., 2023; Peng et al., 2024; Xie et al., 2025).

Polyphenols and phenolic acids represent another critical class of bioactive compounds. Comprehensive phytochemical profiling has identified numerous phenolic acids in the leaves, twigs, and stems of *M. oleifera*, including caffeic acid, chlorogenic acid, cinnamic acid, coumaric acid, ferulic acid, gallic acid, and syringic acid (Pareek et al., 2024). Gallic acid, chlorogenic acid, and ferulic acid are particularly noteworthy for their potent antioxidant properties, with chlorogenic acid and gallic acid representing major constituents (Pareek et al., 2024). The phenolic acid content exhibits considerable variability depending on extraction solvent and plant part, with acetonic extracts identified as a particularly rich source of gallic acid (Pareek et al., 2024).

3.1.2 Glucosinolates and isothiocyanates

Glucosinolates and isothiocyanates constitute a distinctive class of sulphur-containing compounds that are enzymatically hydrolysed by myrosinase to yield bioactive isothiocyanates. Glucomoringin, chemically designated as 4-(α -L-rhamnopyranosyloxy)benzyl glucosinolate, is the principal glucosinolate found in *M. oleifera* seeds and serves as the precursor to the bioactive isothiocyanate moringin (Alidadi et al., 2023; Chodur et al., 2018). Following myrosinase-mediated hydrolysis, glucomoringin yields moringin, chemically designated as 4-(α -L-rhamnopyranosyloxy)benzyl isothiocyanate (Brunelli et al., 2010; Chodur et al., 2018).

The designation “*Moringa* isothiocyanate-1” (MIC-1) is used in the literature to refer specifically to this purified isothiocyanate compound (Jaja-Chimedza et al., 2022; Sailaja et al., 2021). Thus, glucomoringin (GMG) is the glucosinolate precursor, moringin (or GMG-ITC) is the corresponding isothiocyanate, and MIC-1 is the nomenclature applied to the isolated bioactive compound in experimental studies (Brunelli et al., 2010; Jaja-Chimedza et al., 2022).

Moringin has emerged as a particularly potent bioactive compound with significant anti-inflammatory properties. Mechanistic studies have demonstrated that moringin functions as a potent modulator of the nuclear factor-kappa B (NF- κ B) pathway. In lipopolysaccharide (LPS)-induced inflammation models, MIC-1 inhibited the nuclear accumulation of NF- κ B in C2C12 myoblasts, an effect associated with reduced expression of pro-inflammatory markers including TNF- α , IL-1 β , and IL-6 (Jaja-Chimedza et al., 2022). Transcriptomic analysis further revealed

that MIC-1 suppressed LPS-induced inflammation by decreasing nuclear translocation of NF- κ B in skeletal muscle cells (Jaja-Chimedza et al., 2022). The anti-inflammatory mechanisms of MIC-1 involve inhibition of the NF- κ B pathway and activation of Nrf2-mediated antioxidant signalling (Sailaja et al., 2022).

The seeds are a particularly rich source of glucosinolates. The glucomoringin content in *M. oleifera* seeds has been reported to range from 89 to 264 g kg dry matter⁻¹ depending on cultivation location (Chodur et al., 2018). In unroasted moringa seed kernels, glucomoringin content was measured at 43.7 μ mol/g dry weight, while light and medium roasting increased the content to 69.7–127.3 μ mol g dry weight (Liu et al., 2024b). Germination significantly increased glucomoringin content from 61 μ mol g at day⁻¹ 0 to 149 μ mol g at day 14 under optimized conditions (35 °C) (Liu et al., 2024a). These values are expressed consistently in μ mol g dry weight⁻¹ throughout this review to facilitate direct comparison across studies.

2.1.3 Alkaloids

Alkaloids, including spirochin and related compounds, are present in various plant parts, particularly in the roots and bark (Pareek et al., 2024). The root bark contains additional alkaloids, including moringine and moringinine, which act on sympathetic nerve endings and cardiac and smooth muscle (Pareek et al., 2024). Spirochin has been characterised as a potentially toxic alkaloid, and its presence in root tissue raises toxicity concerns that warrant careful consideration (Alidadi et al., 2023; Taha et al., 2025). Consequently, oral consumption of *M. oleifera* root and root bark may not be safe due to these potentially toxic alkaloids, whereas the leaf is considered possibly the safest part for consumption (Canett-Romero et al., 2014; Taha et al., 2025).

Polysaccharides exhibit significant immunomodulatory properties. Water-soluble polysaccharides, including arabinogalactans comprising arabinose and galactose monomers, have been identified in various plant parts. These compounds activate the gut-associated immune system through beneficial modulation of gut microbiota composition and promotion of anti-inflammatory cytokine secretion (Alidadi et al., 2023).

2.1.4 Vitamins and minerals

Vitamins and minerals further augment the nutritional and therapeutic value of *M. oleifera*. The leaves are rich in vitamins A (as β -carotene), C (ascorbic acid), and E (tocopherols), as well as essential minerals including calcium, potassium, magnesium, and zinc (Pareek et al., 2024). Potassium is notably the most abundant mineral in leaf tissue. Ascorbic acid concentrations of 271 mg 100 g⁻¹ and tocopherol levels of 36.9 mg 100 g⁻¹ have been reported in fresh leaves, with appreciable quantities of carotenoids including trans-lutein (approximately 30% of total carotenoids), trans- β -carotene (approximately 18% of total carotenoids), and trans-zeaxanthin (approximately 6% of total carotenoids) (Pareek et al., 2024).

Unless otherwise stated, all vitamin and mineral concentrations reported in this review refer to fresh leaf mass; where values were originally expressed on a dry mass basis, this is indicated explicitly in the text (Pareek et al., 2024). Other phytochemicals, including saponins, terpenoids, and sterols, contribute to the plant's diverse bioactivities. More than one hundred compounds from different parts of *M. oleifera* have been characterised, encompassing alkaloids, flavonoids, anthraquinones, vitamins, glycosides, and terpenes (Alidadi et al., 2023; Pareek et al., 2024).

3.2. Organ-specific distribution and variability

The phytochemical composition of *M. oleifera* exhibits substantial organ-specific variation, with profound implications for both therapeutic application and safety. Leaves represent the most extensively studied plant part, accounting for the majority of investigations. They are the richest source of flavonoids, polyphenols, and glucosinolates, with the highest total phenolic and flavonoid contents observed in leaf tissues (Pareek et al., 2024).

The leaves' exceptional phytochemical density underpins their widespread use in traditional medicine and modern nutraceutical formulations. Chemical profiling of water extracts of *M. oleifera* leaves using UPLC-Q-Exactive Orbitrap-MS identified 42 compounds, including phenolic acids and their derivatives, flavonoids, isothiocyanates, nucleosides, alkaloids, and other constituents (Wang et al., 2024).

A separate study employing Q-Exactive Orbitrap/MS and Triple Quadrupole UPLC-MS identified 105 phenolic compounds and 61 other compounds across leaves, flowers, seeds, and stems, with 59 compounds characterised for the first time in *M. oleifera*; the phenolic composition of leaves was primarily composed of flavonols and phenolic acids (Gao et al., 2025). This discrepancy between 42 and 105 compounds reflects differences in ex-

traction solvent (water versus polar organic fractions), analytical platform, and the scope of compound classes targeted; the number reported by Wang et al. (2024) specifically refers to water extracts, whereas Gao et al. (2025) analysed multiple polar fractions from four plant parts.

Seeds are characterised by high glucosinolate content. In a study of glucosinolate and isothiocyanate content across raw and processed malunggay tissues, seeds contained 48.63–335.28 $\mu\text{mol g}^{-1}$ glucosinolate, significantly higher than the levels found in leaves (3.06–76.41 $\mu\text{mol g}^{-1}$); steamed seeds and raw leaves exhibited the greatest glucosinolate retention (Yu Oh; Comia, 2024). An earlier quantification reported 65.5 $\mu\text{mol glucosinolate g seed}^{-1}$ dry matter, corresponding to approximately 40 mg g or 4% of seed weight⁻¹ (Fahey et al., 2001, as cited in Bennett et al., 2003). Its profile, abundant in isothiocyanates (mainly moringin), makes the seed a useful reservoir of biologically active constituents. Additionally, seeds contain significant polysaccharide concentrations and have been shown to exhibit antimicrobial activities against various microorganisms (Alidadi et al., 2023).

Roots and bark contain alkaloids with potential toxicity concerns. The presence of spirochin in the root and ephedrine-like stimulant alkaloids in the root bark necessitates caution in their medicinal use, particularly at elevated doses (Alidadi et al., 2023). While the ethanolic root bark extract has been shown to contain nutritive phytochemicals with medicinal uses, acute toxicity testing in Albino rats using Lorke's method demonstrated no mortality at the limit single oral dose of 5000 mg kg⁻¹, corresponding to an LD₅₀ > 5000 mg kg⁻¹, indicating that the extract is non-toxic at this single dosage (Nimyel; Lori, 2023).

However, this acute toxicity finding does not preclude the possibility of adverse effects with repeated or prolonged administration, and it contrasts with the toxicity concerns associated with alkaloid constituents; acute and repeated-dose toxicity profiles may differ substantially, and the safety of chronic root bark consumption remains inadequately characterised.

The impact of cultivation conditions, extraction methods, and processing on phytochemical profiles cannot be overstated. Environmental factors, including temperature, rainfall, and soil composition, modulate the biosynthesis and accumulation of secondary metabolites (Pareek et al., 2024). Furthermore, extraction methodology profoundly affects the qualitative and quantitative recovery of bioactive compounds; different solvents, including methanol, ethanol, and water, yield distinct phytochemical profiles with varying bioactivities (Pareek et al., 2024). These variables introduce considerable heterogeneity across studies and products, complicating direct comparisons and clinical translation.

3.3 Bioavailability and pharmacokinetic considerations

Understanding the absorption, distribution, metabolism, and excretion (ADME) profiles of *M. oleifera* bioactives is essential for translating preclinical efficacy into therapeutic applications. Comprehensive pharmacokinetic investigations using UPLC-Q-Exactive Orbitrap-MS have identified 42–43 compounds in *M. oleifera* leaf extracts, including phenolic acids and their derivatives, flavonoids, isothiocyanates, nucleosides, alkaloids, and other constituents (Wang et al., 2024).

Pharmacokinetic studies in rat plasma have revealed that all measured substances reached their maximum concentration within 0.5 hours of oral administration, indicating rapid absorption (Wang et al., 2024). Notably, vicienin-2 exhibited high peak concentration and favourable bioavailability, while kaempferol-3-O-rutinoside demonstrated a longer biological half-life than other components (Wang et al., 2024). These findings provide critical data for subsequent qualitative evaluation and potential clinical applications of *M. oleifera* leaf extracts.

3.3.1 Bioavailability and pharmacokinetic considerations

Bioavailability remains a critical limitation for many polyphenolic compounds. The therapeutic potential of *M. oleifera* bioactives is constrained by poor gastrointestinal absorption, efflux transport, and limited systemic exposure (Alidadi et al., 2023; Chodur et al., 2018). However, the pharmacokinetic behaviour of individual compounds differs substantially and requires compound-specific consideration.

The pharmacokinetic parameters of vicienin-2 have been relatively well characterised. Following intravenous administration in rats (5 mg kg⁻¹), vicienin-2 exhibited an elimination half-life ($t_{1/2}$) of 2.2 ± 0.9 h, indicating rapid elimination (Li et al., 2019). Another study using UPLC-MS/MS reported an even shorter $t_{1/2}$ (24.1 min) and mean residence time (MRT, 35.2 min), together with a high clearance rate (6.4 mL min⁻¹) and volume of

distribution (Vd, 221.9 mL), consistent with rapid distribution and elimination attributable to the compound's high polarity (Gouvea et al., 2017).

Notably, these pharmacokinetic parameters derive from intravenous administration studies rather than oral dosing; the absolute oral bioavailability has not been determined in these investigations. By contrast, under simulated gastrointestinal conditions, the bioavailability of polyphenols from *M. oleifera* leaf extract was reported as 81.5%, compared with 79.1% for the quercetin control; however, these data originate from an *in vitro* simulated digestion model and cannot be equated with *in vivo* absolute bioavailability (Society for Science, 2021).

Nanoformulation strategies have been explored to overcome these bioavailability limitations. Wang et al. (2025) prepared cholesterol-modified chitosan-coated *Moringa A* liposomes (MA-CLs), which exhibited a particle size of 218.25 ± 1.07 nm, a polydispersity index (PDI) of 0.143 ± 0.005 , a zeta potential of 30.64 ± 0.29 mV, an encapsulation efficiency of $85.17 \pm 1.70\%$, and a drug loading of $7.92 \pm 0.16\%$. Compared with conventional liposomes (MA-Ls), MA-CLs more effectively mitigated the burst release of *Moringa A*, thereby enhancing its oral bioavailability (Wang et al., 2025).

This finding indicates that chitosan-modified liposomal systems hold potential for improving the oral delivery of *M. oleifera* bioactive constituents. Enhanced organ-protective efficacy of nanoformulations in cardioprotective, oncological, and antimicrobial models has been reported in a review, representing a strategic direction for translation from crude extracts toward clinical application (Dove Medical Press, 2026).

Table 1 presents a comprehensive inventory of bioactive compounds identified across different organs of *M. oleifera*, categorised by chemical class with their corresponding primary bioactivities and documented molecular targets. The flavonoid class, particularly quercetin, kaempferol, and rutin, emerges as the most extensively characterised, with well-established mechanisms involving cyclooxygenase/lipoxygenase inhibition and NF- κ B pathway modulation (Alidadi et al., 2023).

Phenolic acids, including gallic and chlorogenic acids, demonstrate potent free radical scavenging activities through direct ROS neutralization (Pareek et al., 2024). Notably, moringin, a glucosinolate-derived isothiocyanate, exhibits mechanistically distinct anti-inflammatory activity through NF- κ B pathway modulation and suppression of TNF- α and IL-1 β production (Alidadi et al., 2023; Jaja-Chimedza et al., 2022). The table further reveals important organ-specific distribution patterns: leaves are richest in flavonoids and phenolic acids, seeds are abundant in glucosinolates, while roots and bark contain alkaloids with documented toxicity concerns (Alidadi et al., 2023; Pareek et al., 2024).

Polysaccharides including arabinogalactans exhibit immunomodulatory activities via gut microbiota modulation (Alidadi et al., 2023). Collectively, this phytochemical diversity forms the molecular foundation for *M. oleifera*'s broad therapeutic potential while underscoring the importance of organ-specific selection for desired bioactivities.

Table 1. Phytochemical constituents of *Moringa oleifera* by chemical class, plant part, bioactive constituents, content ranges, and documented molecular targets

Compound	Plant Part	Content Range	Primary Bioactivity	Key Molecular Targets	Reference
Flavonoids					
Quercetin	Leaves	0.207–7.57 mg g ⁻¹ DW	Antioxidant, anti-inflammatory	COX/LOX inhibition; NF- κ B modulation	Leone et al. (2015), as cited in Alidadi et al. (2023)
Kaempferol	Leaves	0.04–4.59 mg g ⁻¹ DW	Antioxidant, anti-inflammatory	COX/LOX inhibition; cytokine modulation	Leone et al. (2015), as cited in ; Alidadi et al. (2023)
Rutin	Leaves, twigs,	Not reported	Antioxidant,	Free radical scavenging;	Leone et al. (2015),

	stems	in primary source	vasoprotective	endothelial protection	as cited in Alidadi et al. (2023)
Vicenin-2	Leaves	Not quantified in <i>M. oleifera</i>	Antioxidant	Intestinal absorption: 40.2 ± 2.5% of dose (oral, 180 mg kg ⁻¹ , rat)	Pareek et al. (2024)
Kaempferol-3-O-rutinoside	Leaves	Not quantified in <i>M. oleifera</i>	Antioxidant	Pharmacokinetic parameters determined in rat plasma after oral administration	Leone et al. (2015), as cited in Alidadi et al. (2023)
Phenolic Acids					
Chlorogenic acid	Leaves	0.018–0.489 mg g ⁻¹ DW	Antioxidant, anti-inflammatory	ROS scavenging; inflammatory mediator suppression	Leone et al. (2015), as cited in
Gallic acid	Leaves	Not reported in primary source	Antioxidant	Free radical scavenging	Pareek et al. (2024)
Ferulic acid	Leaves, twigs	Not reported in primary source	Antioxidant	Free radical neutralization	Pareek et al. (2024)
Caffeic acid	Leaves, twigs, stems	Not reported in primary source	Antioxidant	ROS scavenging	Pareek et al. (2024)
Glucosinolates/Isothiocyanates					
Glucomoringin (GMG)	Leaves	21.84–59.4 mg g ⁻¹ DW	Anti-inflammatory	NF-κB pathway modulation	Amaglo et al. (2010), as cited in
Moringin (MIC-1)	Leaves	1.15% w/w	Anti-inflammatory, antioxidant	NF-κB nuclear translocation inhibition (1 μM, C2C12 myoblasts); TNF-α, IL-1β, IL-6 downregulation	Waterman et al. (2014), as cited in Jaja-Chimedza et al. (2022)
Polysaccharides					
Arabinogalactan (F1)	Gum	Molecular weight 190 kDa	Immunomodulatory, antioxidant	DPPH radical scavenging (dose-dependent); β-lactoglobulin binding	Raja et al. (2016)

Alkaloids

Spirochin	Roots, bark	Not quantified	Bioactive (toxicity concerns)	Not characterised in primary literature	Pareek et al. (2024)
Moringine, moringinine	Root bark	Not quantified	Sympathomimetic activity	Actions on sympathetic nerve endings and cardiac/smooth muscle	Duke (1983), as cited in

Polysaccharides

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Vitamins

Vitamin A (β -carotene)	Leaves	6.8–91.8 mg 100 g ⁻¹	Antioxidant, immune support	ROS neutralization	Sánchez-Machado et al., as cited in
Vitamin C (ascorbic acid)	Leaves	4.5–220 mg 100 g ⁻¹	Antioxidant, immune support	Free radical scavenging	Sánchez-Machado et al., as cited in
Vitamin E (tocopherols)	Leaves	9.0–122.2 mg 100 g ⁻¹	Antioxidant	Lipid peroxidation inhibition	Sánchez-Machado et al., as cited in

Minerals

Potassium	Leaves	1317–2025 mg 100 g ⁻¹	Cardiovascular support	Electrolyte balance	Sánchez-Machado et al., as cited in
Calcium	Leaves	147.4–7230 mg 100 g ⁻¹	Multiple physiological functions	Enzyme cofactor; structural roles	Sánchez-Machado et al., as cited in
Magnesium	Leaves	5.6–13.8 mg 100	Multiple physiological	Enzyme cofactor	Sánchez-Machado

		g ⁻¹	functions	et al., as cited in
Zinc	Leaves	0.05–3.1 mg 100 g ⁻¹	Multiple physiological functions	Sánchez-Machado et al., as cited in

Note: Abbreviations: COX, cyclooxygenase; LOX, lipoxygenase; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species; DW, dry weight; DPPH, 2,2-diphenyl-1-picrylhydrazyl. Source: Authors, 2026.

Figure 1 shows reported concentrations of major bioactive compound classes in *M. oleifera* across plant parts. Total phenolics (44.3 mg GAE g⁻¹ DW) and total flavonoids (25.6 mg QE g⁻¹ DW) predominate in leaves, confirming leaves as the richest source of phenolic antioxidants. Glucosinolates are higher in seeds (65.5 mg g⁻¹ DW) than in leaves (40.6 mg g⁻¹ DW), supporting the seed as the principal reservoir of glucomoringin and its derived isothiocyanate moringin (11.5 mg g⁻¹ DW equivalent in leaves). Roots and bark contain 12.4 mg g⁻¹ DW total alkaloids, consistent with documented toxicity concerns. Potassium (2025 mg 100 g⁻¹ DW) and vitamin C (220 mg 100 g⁻¹ FW) are abundant in leaves, supporting cardiovascular and antioxidant functions.

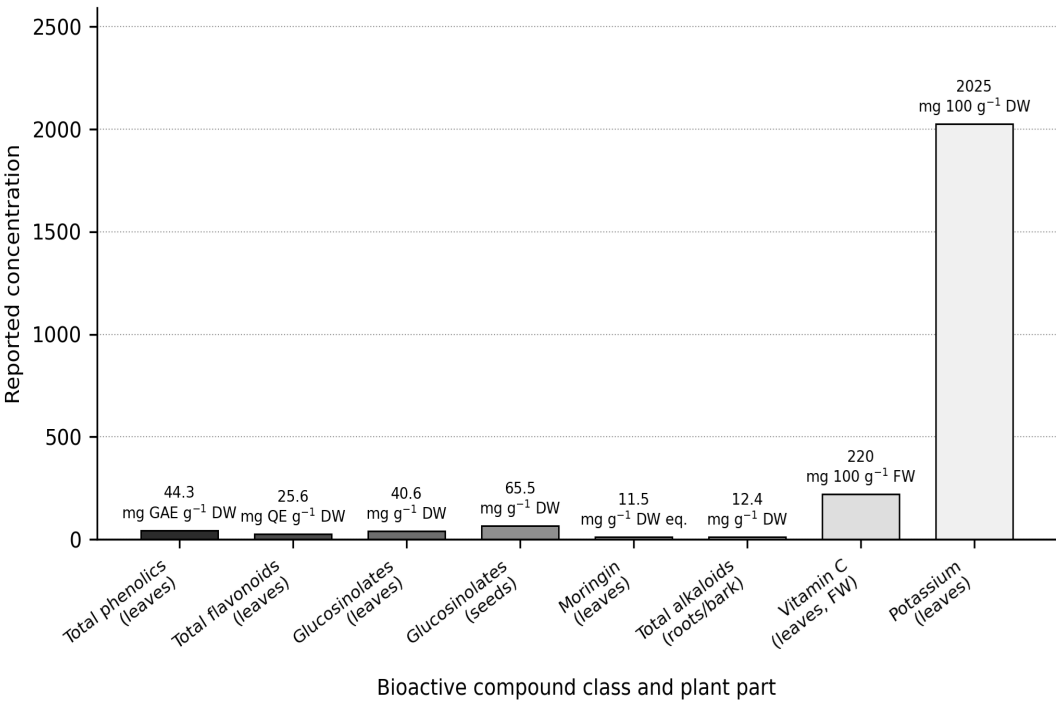


Figure 1. Bioactive compound classes and plant parts of *Moringa oleifera*. Source: Authors, 2026.

Figure 2 integrates the principal signalling pathways through which *M. oleifera* phytochemicals exert cardioprotective and immunomodulatory effects. Flavonoids (quercetin, kaempferol) and isothiocyanates (moringin, MIC-1) converge on the NF-κB module, inhibiting IKK-mediated IκB-α degradation and p65 nuclear translocation, thereby suppressing TNF-α, IL-1β, IL-6, and MCP-1. Isothiocyanates and polyphenols activate the Keap1–Nrf2–ARE axis, upregulating SOD, CAT, GSH, and HO-1 while promoting IL-10. Polyphenols additionally inhibit the arachidonic acid cascade (COX-2/PGE₂) and iNOS, reducing vascular inflammation and improving endothelial function. Evidence levels are annotated per node: predominantly preclinical [P], with clinical support [C] for cytokine suppression in HIV populations and modest endothelial effects

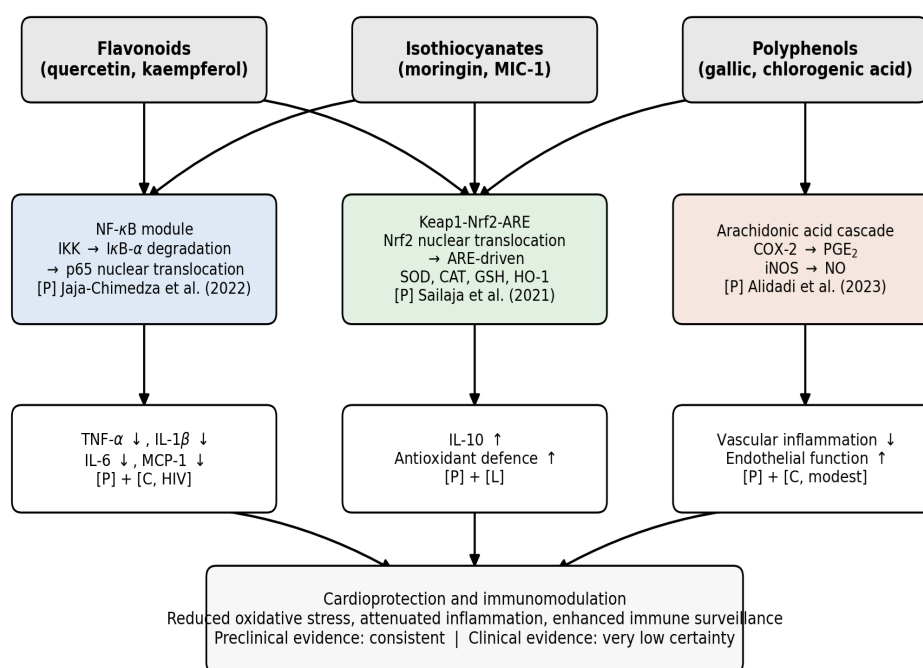


Figure 2. Integrated signalling pathways of *Moringa oleifera* phytochemicals showing NF-κB, Keap1–Nrf2–ARE, and COX-2/iNOS nodes with evidence levels. Source: Authors, 2026.

4. Cardioprotective Mechanisms: From Molecular Pathways to Physiological Outcomes

4.1 Modulation of key signaling pathways in cardiovascular protection

NF-κB pathway inhibition represents a central mechanism whereby *M. oleifera* exerts its anti-inflammatory cardioprotective effects. Activation of nuclear factor-kappa B (NF-κB) drives the transcription of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1), which perpetuate vascular inflammation and promote atherosclerotic progression. *M. oleifera* extracts suppress NF-κB activation through direct downregulation of the pathway or indirect effects mediated by changes in intestinal tissue integrity and gut microbiome composition (Alidadi et al., 2023). Isothiocyanates, particularly moringin, inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-1β (Alidadi et al., 2023).

Nrf2/Keap1 pathway activation constitutes a second critical mechanism, enhancing endogenous antioxidant defences. *M. oleifera* upregulates nuclear factor erythroid 2-related factor 2 (Nrf2), which results in increased transcription of antioxidant and cytoprotective genes (Frontiers, 2022). This pathway activation leads to elevated expression of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione, thereby neutralising reactive oxygen species (ROS) and mitigating oxidative stress-induced tissue damage. The Nrf2-activating properties of *M. oleifera* are largely attributable to isothiocyanates, particularly moringin, which functions as a potent inducer of phase II detoxifying enzymes (Alidadi et al., 2023).

PI3K/Akt pathway modulation promotes cell survival and inhibits apoptosis in cardiac tissue. Shi et al. (2025) employed a Sprague–Dawley rat model of acute myocardial infarction (AMI) and administered an ethanolic extract of *M. oleifera* leaves (EE-MO) by gavage at low (5 mg kg⁻¹), medium (30 mg kg⁻¹), and high (60 mg kg⁻¹) doses. Compared with the model group, the medium- and high-dose groups showed reduced left ventricular internal dimension at systole (LVIDs) and increased left ventricular ejection fraction (LVEF) and fractional shortening (FS) ($p < 0.05$); myocardial p-PI3K/PI3K and p-Akt/Akt ratios were elevated, while IL-6, IL-1β, and TNF-α levels were reduced ($p < 0.05$). These findings derive from a rat model and have not been validated in humans.

AMPK activation improves cellular energy homeostasis and metabolic regulation. Xie et al. (2018) used 3T3-L1 preadipocytes and a mouse model treated with a petroleum ether extract of *M. oleifera* leaves (MOPEE). *In vitro*,

MOPEE inhibited adipogenesis through AMPK pathway activation, promoting ACC phosphorylation and downregulating SREBP1c and FAS expression. Ganjavi et al. (2023) isolated rutin (quercetin-3-*O*-rutinoside) from *M. oleifera* leaves and treated 3T3-L1 adipocytes at 40 µg mL⁻¹, observing significant inhibition of adipogenesis (79.9%), enhanced glucose uptake, increased AMPK phosphorylation, a 1.31-fold increase in Glut-4 expression, and a 0.73-fold decrease in PPAR-γ expression ($p < 0.05$). All of this evidence derives from cell and animal models.

PPAR modulation regulates lipid metabolism and anti-inflammatory gene expression. Almatrafi et al. (2017) used a guinea pig model of high-cholesterol-diet-induced hepatic steatosis, feeding diets containing 10% (low-dose) or 15% (high-dose) *M. oleifera* leaves. The high-dose group showed significantly lower hepatic triglyceride and cholesterol concentrations ($p < 0.001$), reduced PPAR-γ and DGAT-2 gene expression ($p < 0.005$), and lower IL-1β and IFN-γ protein concentrations. This study was conducted in guinea pigs and has not been confirmed in humans.

MAPK pathway attenuation reduces stress-responsive signalling cascades. A study using a CCl₄-induced hepatic fibrosis rat model showed that gavage administration of an ethanolic extract of *M. oleifera* leaves inhibited p38-MAPK phosphorylation and reduced TNF-α expression, thereby decreasing hepatic stellate cell activation and collagen deposition. Mohamad et al. (2025), in a doxorubicin-induced cardiotoxicity rat model, further demonstrated that *M. oleifera* leaf extract-loaded niosomes (MOE-NIO, 250 mg kg⁻¹, gavage) downregulated p38 MAPK expression while upregulating Nrf2, attenuating oxidative stress and inflammation. These mechanistic findings derive from animal models, and their relevance to humans remains unclear.

The consistent preclinical modulation of PI3K/Akt, AMPK, PPAR, and MAPK pathways (all in rodent or cell models) contrasts sharply with the very low certainty of clinical evidence for cardiometabolic outcomes. This discordance is not incidental: it reflects the fundamental translation barriers, poor oral bioavailability, absence of dose-finding studies, and the gap between *in vitro* concentrations and achievable plasma levels that this review identifies as the central obstacle to clinical translation.

4.2 Antihypertensive effects

Hypertension remains a leading preventable risk factor for cardiovascular disease and all-cause mortality worldwide. *Moringa oleifera* has garnered attention as a potential natural antihypertensive agent, with multiple mechanisms contributing to blood pressure reduction (Dewadas et al., 2026).

Angiotensin-converting enzyme (ACE) inhibition represents a primary mechanism. Four novel ACE-inhibitory peptides IPPAYSK, ILVDR, FFFPK, and LLDPR were identified from *M. oleifera* leaves, with IC₅₀ values of 116.06, 81.25, 510.67, and 277.16 µM, respectively. Ma et al. (2021) isolated two dual ACE–renin inhibitory peptides, LGF (IC₅₀ = 0.29 ± 0.13 mM) and GLFF (IC₅₀ = 0.31 ± 0.04 mM), from the <1 kDa ultrafiltration fraction of leaf protein; oral administration to spontaneously hypertensive rats reduced systolic blood pressure by 19.4 mmHg and 18.2 mmHg, respectively. The seed-derived peptide QGPRPQ demonstrated ACE-inhibitory activity (IC₅₀ = 1.15 ± 0.3 mM). In addition, Darwish et al. (2024) reported an ACE-inhibitory IC₅₀ of 104.4 µg/mL for *M. oleifera* leaf extract, with the isolated compound 4-*O*-caffeoylquinic acid showing an IC₅₀ of 62.92 µM.

The effects of ACE inhibition have been validated *in vivo* in animal models. Aekthammarat et al. (2019) employed an L-NAME-induced hypertensive rat model and administered an aqueous extract of *M. oleifera* leaves (MOE) by gavage at 30 and 60 mg kg day⁻¹, observing dose-dependent reductions in blood pressure and heart rate; in isolated mesenteric arterial beds, MOE (0.001–0.3 mg) produced dose-dependent relaxation that was abolished by endothelial denudation. Mechanistic studies further indicated that the vasorelaxant effect of MOE involves endothelium-derived hyperpolarizing factor (EDHF)-mediated hyperpolarization and calcium channel blockade.

Vasodilation through increased nitric oxide (NO) synthesis reduces vascular resistance. Bioactive constituents of *M. oleifera* promote vasodilation by enhancing NO synthesis and inhibiting ACE, thereby reducing vascular resistance. Regarding clinical evidence, a meta-analysis of nine randomised controlled trials ($N \approx 649$) reported a modest reduction in diastolic blood pressure (SMD: -0.41; 95% CI: -0.75 to -0.07; $p = 0.02$; $I^2 = 19\%$), although this effect was not robust in sensitivity analyses (Crisan et al., 2025). Subgroup analyses suggested potential benefits at doses below 10 g/day, in participants under 50 years of age, and in interventions lasting 12 weeks or longer (Crisan et al., 2025). A systematic review of clinical antihypertensive efficacy noted that, although

limited literature suggests *M. oleifera* leaf supplementation may lower blood pressure in hypertensive individuals, methodological deficiencies limit confidence in these findings (David, et al. 2025; Dewadas, et al. 2026).

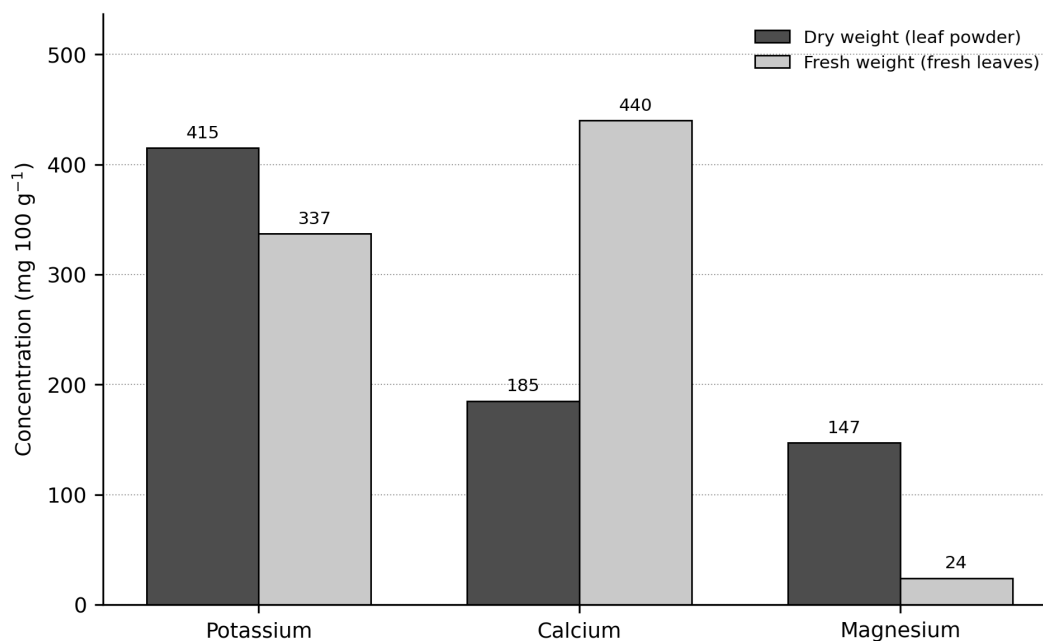


Figure 3. Reported potassium, calcium, and magnesium concentrations in *Moringa oleifera* leaves on dry-weight and fresh-weight bases. Source: Authors, 2026.

Figure 3 compares potassium, calcium, and magnesium concentrations in *M. oleifera* leaves reported on two different bases. In dry leaf powder, Sánchez-Machado et al. (2010) reported potassium, calcium, and magnesium concentrations of 415, 185, and 147 mg 100 g⁻¹ dry weight, respectively. In fresh leaves, Oduro et al. (2008) reported corresponding values of 337 mg 100 g⁻¹ potassium, 440 mg 100 g⁻¹ calcium, and 24 mg 100 g⁻¹ magnesium on a fresh weight basis. The marked discrepancy between the two datasets reflects the concentrating effect of drying, which typically increases mineral concentrations 8–10-fold per unit mass. Notably, calcium is higher in fresh leaves than in leaf powder in these two datasets, indicating that direct comparison is confounded by cultivar, soil composition, harvest stage, and analytical method. Sample size and dispersion were not reported in either source study.

4.2.1 Mineral contribution to blood pressure regulation

The electrolyte profile of *M. oleifera* leaves has been proposed to contribute to blood pressure regulation (Menichetti et al., 2025). Sánchez-Machado et al. (2010) reported potassium, calcium, and magnesium concentrations of 415, 185, and 147 mg 100 g⁻¹ dry weight, respectively, in dried leaf powder; Oduro et al. (2008) reported corresponding values of 337, 440, and 24 mg 100 g⁻¹ fresh weight in fresh leaves. However, the actual contribution of these minerals to daily intake at typical supplementation doses is modest.

At a commonly used dose of 5 g leaf powder per day, the potassium provided would be approximately 20.8 mg, representing only about 0.6% of the WHO-recommended daily potassium intake of 3,500 mg for adults (WHO, 2012). Even at a higher dose of 10 g day⁻¹, the contribution remains below 1.2% of the recommended intake. Consequently, the mineral content of *M. oleifera* leaf powder is unlikely to account for any antihypertensive effect observed in clinical trials, and the putative mineral-mediated mechanism should be regarded as negligible at usual supplemental doses.

4.2.2 Clinical evidence for blood pressure-lowering effects

Clinical evidence for the blood pressure-lowering effects of *M. oleifera* remains methodologically limited and internally inconsistent. The most rigorous synthesis to date, a meta-analysis of nine randomised controlled trials (12 study arms; 649 participants: 341 intervention, 308 control), reported a modest reduction in diastolic blood pressure (SMD: -0.41 ; 95% CI: -0.75 to -0.07 ; $p = 0.02$; $I^2 = 19\%$); however, this effect was not robust in sensitivity analyses (Crişan et al., 2025).

The same meta-analysis found no statistically significant effect on systolic blood pressure (SMD: -0.13 ; 95% CI: -0.39 to 0.13 ; $p = 0.33$), and no significant effects on most other cardiometabolic outcomes, including fasting glucose, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (Crişan et al., 2025). Subgroup analyses suggested potential benefit at doses below 10 g day^{-1} , in participants under 50 years of age, and in interventions lasting 12 weeks or longer, although these findings require confirmation in adequately powered trials (Crişan et al., 2025).

Methodological limitations across the included trials include poor quality of blood pressure assessment, lack of randomization and blinding in several studies, substantial heterogeneity in dosing and preparation, and considerable variability in sample sizes (Crişan et al., 2025). Notably, the certainty of evidence for all evaluated cardiometabolic outcomes was graded as very low using the GRADE framework (Crişan et al., 2025). Therefore, further adequately powered randomised controlled trials with standardised preparations and clinically meaningful endpoints are required before *M. oleifera* can be promoted for therapeutic blood pressure reduction.

4.3 Lipid profile modulation and anti-atherosclerotic effects

Dyslipidaemia is a major risk factor for atherosclerosis and cardiovascular disease. Preclinical studies have examined the effects of *M. oleifera* on lipid metabolism, although clinical evidence for lipid modulation in humans remains inconsistent and of very low certainty.

4.3.1 Preclinical evidence

In animal models, *M. oleifera* preparations have demonstrated lipid-lowering effects. Mehta et al. (2003) reported that oral administration of *M. oleifera* fruit ($200 \text{ mg kg}^{-1} \text{ day}^{-1}$) to hypercholesterolaemic rabbits for 120 days reduced serum total cholesterol, phospholipids, triglycerides, VLDL, and LDL, and increased the HDL ratio compared with controls, with effects comparable to lovastatin ($6 \text{ mg kg}^{-1} \text{ day}^{-1}$). Helmy et al. (2017) demonstrated that feeding high-fat-diet rats with *M. oleifera* leaf powder (0.737% of diet) or dry leaf extract (400 mg kg^{-1} body weight) for 60 days alleviated high-fat-diet-induced elevations in serum cholesterol, triglycerides, LDL cholesterol, and malondialdehyde. Omodanisi et al. (2017) reported that methanolic leaf extract (250 mg kg^{-1}) administered to streptozotocin-induced diabetic rats for 42 days normalised lipid profile parameters compared with untreated diabetic controls.

In vitro, a methanolic leaf extract exhibited concentration-dependent cholesterol-binding activity, reaching 62.35% inhibition at $300 \mu\text{g mL}^{-1}$ in a cholesterol-binding assay, compared with 72.24% for the standard drug cholestyramine. This mechanism may contribute to reduced intestinal cholesterol absorption.

Regarding HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, evidence comes primarily from *in vitro* and *in silico* studies rather than direct enzymatic IC_{50} determinations. Tabboon et al. (2016) demonstrated that a phenolics-enriched *M. oleifera* extract ($100\text{--}400 \mu\text{g mL}^{-1}$) significantly decreased intracellular cholesterol in HepG2 cells and reduced HMG-CoA reductase mRNA expression, with the extract containing 202.3 mg g^{-1} total phenolics, including isoquercetin (80.23 mg g^{-1}) and quercitrin (62.48 mg g^{-1}). Ready et al. (2012) reported that *M. oleifera* polyphenols at $200\text{--}400 \mu\text{g}$ inhibited HMG-CoA reductase activity in rat liver microsomes, with $400 \mu\text{g}$ being most potent ($10.26 \pm 0.33 \text{ nmol mg protein}^{-1} \text{ coenzyme A}^{-1}$ released versus $18.87 \pm 0.12 \text{ nmol mg protein}^{-1}$ in controls).

Berjawi (2025) used *in silico* molecular docking to demonstrate that quercetin and myricetin primarily occupy the NADPH binding site of HMG-CoA reductase, suggesting an alternative mechanism of enzyme modulation distinct from that of simvastatin, which competitively binds the active site. *In vitro*, MO extract (0.03%) reduced cholesterol levels by 58% in HepG2 cells compared with 20% for simvastatin alone, with the combination achieving 70% reduction. However, direct enzymatic IC_{50} values for HMG-CoA reductase inhibition by *M. oleifera* constituents have not been reported in the retrieved literature; the available evidence is limited to docking predictions, cellular gene-expression data, and microsomal activity assays.

4.3.2 Clinical evidence

Clinical evidence for lipid modulation by *M. oleifera* in humans is inconsistent. The most comprehensive synthesis, a meta-analysis of nine RCTs (12 study arms; 649 participants), found no statistically significant effects of moringa supplementation on total cholesterol (SMD: -0.20; 95% CI: -0.76 to 0.35; $p = 0.47$; $I^2 = 81\%$), LDL cholesterol (SMD: -0.30; 95% CI: -1.10 to 0.51; $p = 0.47$; $I^2 = 91\%$), HDL cholesterol (SMD: 0.18; 95% CI: -0.60 to 0.96; $p = 0.65$; $I^2 = 90\%$), or triglycerides (SMD: -0.14; 95% CI: -0.71 to 0.44; $p = 0.64$; $I^2 = 82\%$) (Crişan et al., 2025). The certainty of evidence was graded as very low for all lipid outcomes (Crişan et al., 2025). Subgroup analyses suggested potential benefit for triglycerides at doses below 10 g day⁻¹ and for interventions lasting 12 weeks or longer, but these findings require confirmation in adequately powered trials (Crişan et al., 2025).

A single RCT in type 2 diabetic subjects ($n = 40$) reported that 60 g day⁻¹ moringa leaves for 14 days significantly increased triglyceride values (from 123.80 ± 53.69 to 151.20 ± 41.47 mg dL⁻¹; $p = 0.04$), an adverse rather than beneficial effect, and after adjusting for pre-intervention values, there was no significant difference in any parameter (Afiaenyi et al., 2025). This small trial contrasts with the pooled meta-analytic findings and underscores the inconsistency of clinical lipid data.

In summary, preclinical studies demonstrate consistent lipid-lowering effects of *M. oleifera* in animal models and cholesterol-binding activity *in vitro*. However, clinical evidence does not support consistent lipid modulation in humans, and the certainty of evidence is very low. The putative mechanism of HMG-CoA reductase inhibition remains supported only by *in silico* docking, microsomal activity assays, and cellular gene-expression data, without reported enzymatic IC₅₀ values.

4.4 Antioxidant and anti-inflammatory cardioprotection

Doxorubicin (DOX) is a potent anthracycline chemotherapeutic agent whose clinical utility is limited by dose-dependent cardiotoxicity. Preclinical studies have investigated whether *M. oleifera* extracts can mitigate DOX-induced cardiac injury.

4.4.1 Preclinical evidence in animal models

Mohamad et al. (2025) examined the cardioprotective effect of ethanolic *M. oleifera* leaf extract loaded into niosomes (MOE-NIO) against DOX-induced cardiotoxicity in male Wistar rats ($n = 70$, seven groups of 10). DOX was administered intraperitoneally at 4 mg kg⁻¹ once weekly for four weeks; MOE or MOE-NIO was given orally at 250 mg kg⁻¹ daily for four weeks, either co-administered with DOX or pre-administered one week before DOX injection (Mohamad et al., 2025). Pre- and co-treatment with MOE-NIO significantly mitigated DOX-induced cardiotoxicity, as evidenced by reduced serum aspartate aminotransferase, creatine kinase-MB, lactate dehydrogenase, and cardiac troponin I levels (Mohamad et al., 2025).

MOE-NIO also alleviated lipid peroxidation (malondialdehyde) and nitrosative stress (nitric oxide), and reduced inflammatory markers including myeloperoxidase and tumour necrosis factor- α , while restoring glutathione content and superoxide dismutase activity (Mohamad et al., 2025). Mechanistically, MOE-NIO neutralized DOX-upregulated NF- κ B and p38 MAPK expression and restored DOX-downregulated Nrf2 expression in cardiac tissue (Mohamad et al., 2025).

Patintingan et al. (2023) evaluated the cardioprotective effect of *M. oleifera* leaf aqueous extract via mitochondrial biogenesis pathways in male Sprague-Dawley rats ($n = 24$, four groups of six). DOX was administered intraperitoneally at 4 mg kg⁻¹ once weekly for four weeks (total dose 16 mg kg⁻¹), with *M. oleifera* extract given orally at 200 or 400 mg kg⁻¹ daily for 28 days (Patintingan et al., 2023). The extract decreased LDH and CK-MB, malondialdehyde levels, and glutathione peroxidase activity (Patintingan et al., 2023). These changes aligned with reduced caspase-3 mRNA expression, increased mRNA expression of PGC-1 α and Nrf2, and elevated mitochondrial DNA copy number (Patintingan et al., 2023). However, *M. oleifera* extract did not influence SOD2 mRNA expression or 8-OH-dG levels (Patintingan et al., 2023).

Gouda et al. (2023) evaluated *M. oleifera* nanoparticles (MONPs) in DMBA-induced breast cancer rats treated with DOX ($n = 49$ albino rats). Rats treated synergistically or prophylactically with MONPs and DOX showed significant reductions in cardiotoxicity markers and increases in antioxidant markers, alongside reduced tumour markers (Gouda et al., 2023). The authors concluded that prophylactic use of MONPs and synergistic use with

DOX induced resistance against DOX-induced cardiotoxicity and ameliorated breast cancer aggressiveness and oxidative stress (Gouda et al., 2023).

4.4.2 Antioxidant–chemotherapy interaction: A critical consideration

A critical caveat applies to the interpretation of these cardioprotective findings. DOX exerts its antitumour activity partly through reactive oxygen species generation, and antioxidant co-administration may theoretically interfere with its cytotoxic efficacy against cancer cells. Evidence from *M. oleifera*–DOX combination studies is conflicting.

Zunica et al. (2021) evaluated *M. oleifera* seed extract concentrate in combination with chemotherapy (DOX plus cyclophosphamide) in immunocompromised female mice with diet-induced obesity bearing MDA-MB-231-derived xenograft tumours. *Moringa* supplementation alone did not attenuate tumour growth relative to chemotherapy alone, and in combination worsened tumour progression; moringa supplementation alone reduced angiogenesis, but this effect was abrogated in combination with chemotherapy (Zunica et al., 2021). The authors cautioned that moringa seed extract consumption during breast cancer chemotherapy may have a negative interaction and recommended caution (Zunica et al., 2021).

By contrast, Gouda et al. (2023) reported that MONPs and DOX combination reduced tumour markers and cardiotoxicity markers, suggesting a potential synergistic benefit. These discordant findings indicate that the safety of combining *M. oleifera* with DOX cannot be assumed and may depend on plant part (leaf versus seed), extract preparation, tumour type, and host metabolic status.

4.4.3 Summary

Preclinical studies demonstrate that *M. oleifera* leaf extracts and nanoformulations can mitigate DOX-induced cardiotoxicity through antioxidant, anti-inflammatory, and mitochondrial biogenesis pathways in rodent models (Gouda et al., 2023; Mohamad et al., 2025; Patintingan et al., 2023). However, evidence regarding the impact on antitumour efficacy is conflicting, with seed extract showing a negative interaction with chemotherapy in one model (Zunica et al., 2021). Until adequately powered studies clarify whether *M. oleifera* modulates DOX antitumour efficacy in humans, the cardioprotective findings from animal models should not be translated into clinical recommendations for adjunctive use during DOX chemotherapy.

4.5 Preclinical evidence base

Figure 4 shows the distribution of primary studies cited in this review by evidence tier and research domain. Cardioprotection is dominated by *in vivo* animal studies (n = 8), with fewer *in vitro* (n = 2), clinical (n = 2), and nanoformulation (n = 1) investigations, reflecting the predominantly preclinical mechanistic focus of this field. Immunomodulation is more balanced across *in vitro* (n = 3), animal (n = 2), and clinical (n = 2) tiers. Phytochemistry and bioavailability comprise mainly *in vitro* (n = 4) and animal (n = 3) studies, with one nanoformulation study. Clinical outcomes are represented exclusively by human evidence (n = 3), comprising randomised trials, a systematic review, and a meta-analysis. Notably, the figure reports the number of cited studies, not the strength or certainty of evidence; certainty was graded very low for cardiometabolic outcomes. The sparse clinical tier across all domains underscores the translational gap.

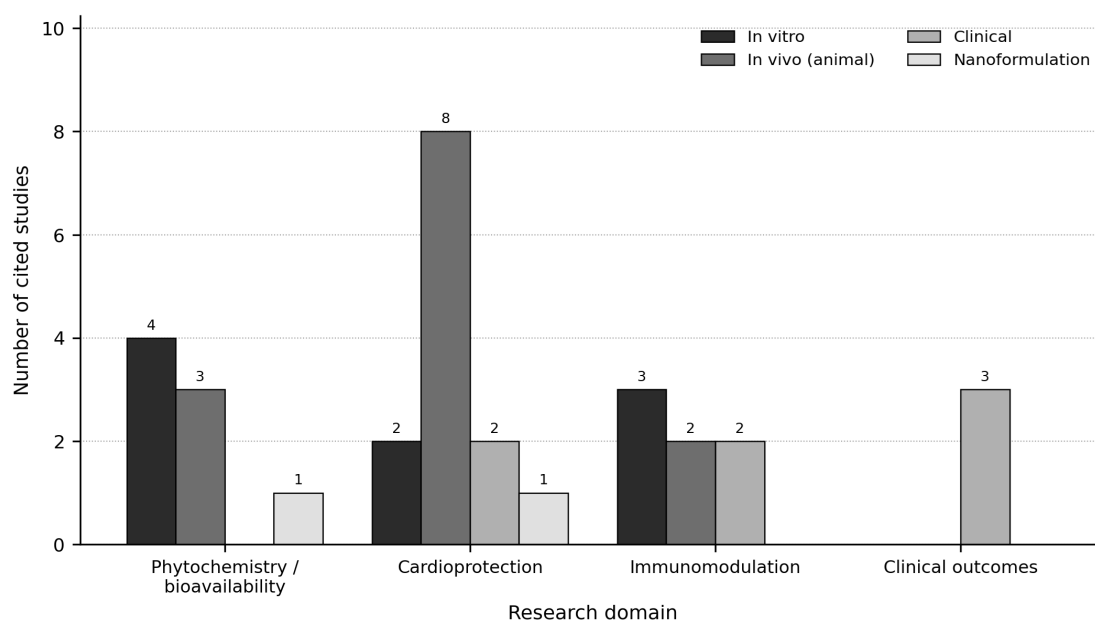


Figure 4. Distribution of primary studies cited in this review by evidence tier and research domain. Source: Authors, 2026.

The consistent demonstration of cardioprotective efficacy across multiple experimental models, including ischemia-reperfusion injury, doxorubicin-induced cardiotoxicity, hypertension, and hyperlipidemia, provides strong mechanistic evidence for the therapeutic potential of *M. oleifera* (Mehta et al., 2026). *Moringa oleifera* enhances insulin sensitivity, regulates lipid profiles and blood pressure, reduces inflammation, and protects against oxidative damage (Villegas-Vazquez et al., 2025). However, while preclinical studies support its efficacy, large-scale clinical trials, standardized formulations, and advanced delivery methods are needed to optimize its therapeutic potential (Mehta et al., 2026; Villegas-Vazquez et al., 2025).

4.6 Nanoformulation advances

Despite the promising preclinical evidence, the therapeutic translation of *M. oleifera* bioactives is constrained by poor oral bioavailability, limited gastrointestinal absorption, and rapid metabolism (Mehta et al., 2026). Nanoformulation strategies have emerged as promising approaches to overcome these limitations (Mehta et al., 2026).

The potential for targeted delivery and controlled release offers additional advantages. Coating *Moringa* bioactives with polymers or lipids enhances stability and controls release, reducing degradation of heat- and light-sensitive compounds, thereby improving shelf life and bioavailability (*M. oleifera* Tablets: A Comprehensive Review, 2025).

Nanoformulations improve *M. oleifera* stability and compound bioavailability (An insight review, 2025). Novel formulation techniques designed to maximise bioavailability have been comprehensively analysed (*Moringa oleifera* Tablets: A Comprehensive Review, 2025). While these advances are encouraging, rigorously designed clinical studies are urgently required to validate their safety, effectiveness, and translational value in CVD management (Mehta et al., 2026).

5. Immunomodulatory Mechanisms: Cellular and Molecular Regulation

5.1 Cytokine modulation

Concurrently, *M. oleifera* exerts significant inhibition of pro-inflammatory enzymes. Studies have shown that treatment with *M. oleifera* fractions results in the downregulation of iNOS, COX-2, and NF- κ B expression, while upregulating I κ B α levels. The inhibition of iNOS and COX-2 is particularly noteworthy, as these enzymes

are critical mediators of inflammatory cascades that contribute to chronic immune dysfunction. *M. oleifera* significantly reduces inflammatory markers, including IL-1, IL-6, TNF- α , and COX-2.

The anti-inflammatory profile of *M. oleifera* is further characterised by the promotion of anti-inflammatory cytokines, particularly interleukin-10 (IL-10). The immunomodulatory activity is mediated via multiple pathways, including the promotion of anti-inflammatory cytokine secretion (e.g., IL-10) and the inhibition of pro-inflammatory enzymes such as COX-2.

5.2 Immune cell regulation

Moringa oleifera exerts profound regulatory effects on both innate and adaptive immune cell populations, modulating their proliferation, activity, and functional polarization. Natural killer (NK) cell cytotoxicity is significantly enhanced by *M. oleifera*. Studies indicate that *M. oleifera* can modulate the TME by enhancing NK cell cytotoxicity. Research has demonstrated that *M. oleifera* Lam. leaf ethanol extract can increase NK cell activity in mouse models. NK cell activity peaked at specific concentrations in immunostimulation studies.

Regulatory T cells (Tregs) are modulated by *M. oleifera* through reduction of Treg polarisation in the tumour microenvironment. A deeper understanding of how *M. oleifera* modulates $\gamma\delta$ T cells, natural killer T cells, and mucosal-associated invariant T cells, and their roles in immune-regulatory circuits within the TME, will be critical to advance *M. oleifera* from traditional medicine toward evidence-based immunotherapy and cancer interventions.

5.3 Polysaccharide-mediated immunomodulation

Moringa-derived arabinogalactans, water-soluble polysaccharides comprising arabinose and galactose monomers, represent key immunomodulatory polysaccharides. These compounds exert significant immunomodulatory effects by modulating cytokine production and immune cell activity. A high-purity polysaccharide from *M. oleifera* leaf (MOLP-PE) has been identified, and its structural characteristics and immunomodulatory activity have been investigated.

The activation of the gut-associated immune system via microbiota modulation represents a primary mechanism of polysaccharide-mediated immunomodulation. *Moringa*-derived arabinogalactans activate the gut-associated immune system through beneficial modulation of gut microbiota composition, increasing genera such as *Muribaculaceae* and *Lactobacillus*.

Promotion of anti-inflammatory cytokine secretion and inhibition of COX-2 are central to the immunomodulatory activity of *M. oleifera* polysaccharides. The immunomodulatory activity is mediated via multiple pathways, including the promotion of anti-inflammatory cytokine secretion (e.g., IL-10) and the inhibition of pro-inflammatory enzymes such as COX-2.

Potential therapeutic benefits for metabolic disorders and gut health are emerging from research on *M. oleifera* polysaccharides. Polysaccharides derived from *M. oleifera* exhibit multiple bioactivities, including immune regulation, anti-inflammatory activity, gut microbiota modulation, and antioxidant effects, thereby indicating their significant value in promoting health and preventing diseases. High-purity polysaccharides have shown strong glycolipid absorption inhibitory activity and prebiotic effects on human gut probiotics related to glycolipid metabolism.

5.4 Antioxidant-immune axis

The interplay between oxidative stress and immune dysfunction is well-established, and *M. oleifera* exerts its immunomodulatory effects in part through the enhancement of endogenous antioxidant defences. *M. oleifera* exhibits potent antioxidant capabilities by enhancing endogenous defences, neutralising reactive oxygen species, and mitigating oxidative stress-induced tissue damage. These findings underscore *M. oleifera*'s potential to enhance disease resistance and immune function.

Neutralization of ROS and mitigation of oxidative stress-induced immune dysfunction is achieved through the plant's rich phytochemical content. *M. oleifera* induces expression of Nrf2, the factor controlling transcriptional up-regulation of antioxidative and cytoprotective gene families. The plant contains several bioactive compounds, predominantly isothiocyanate moringin and polyphenols, which are potent inducers of NRF2. Pharmacological

activation of NRF2 by *M. oleifera* leaves protects against diseases by inhibiting oxidative and inflammatory injury.

Reduction of oxidative stress as a driver of chronic inflammation and immune dysregulation is a critical mechanism. *Moringa* isothiocyanate-1 (MIC-1) reduces inflammation and oxidative stress through NF- κ B and Nrf2-mediated anti-inflammatory/antioxidant signalling pathways. MIC-1 affects inflammation and oxidative stress, two key processes involved in the etiology of many chronic diseases, through upstream regulation of two key transcriptional factors. By reducing oxidative stress, *M. oleifera* breaks the vicious cycle of chronic inflammation and immune dysregulation that characterizes many chronic diseases.

5.5 Integration of cardio-immunomodulation

The convergence of cardiovascular and immune dysfunction is increasingly recognised, and *M. oleifera* offers a unique opportunity for dual therapeutic targeting. Shared mechanistic pathways: oxidative stress and inflammation as common drivers of both cardiovascular and immune dysfunction are addressed by *M. oleifera*'s multifaceted bioactivity. *M. oleifera*'s ability to modulate oxidative stress and inflammation, key drivers of chronic diseases, highlights its significant role in disease prevention and treatment. The plant enhances insulin sensitivity, regulates lipid profiles and blood pressure, reduces inflammation, and protects against oxidative damage.

Dual targeting through Nrf2 activation, NF- κ B inhibition, and cytokine modulation enables *M. oleifera* to simultaneously address cardiovascular and immune pathology. By activating Nrf2, the plant enhances endogenous antioxidant defences; by inhibiting NF- κ B, it suppresses pro-inflammatory cytokine production; and by modulating cytokine balance, it promotes anti-inflammatory signalling. *Moringa* is rapidly becoming a key and effective component in formulating healthy foodstuffs because of its outstanding anti-inflammatory, antimicrobial, antidiabetic, antioxidant, and neuroprotective activities.

5.5.1 Preclinical evidence: Combination formulation studies

Quagliariello et al. (2022) evaluated a combined formulation of *Spirulina*, *Ganoderma lucidum*, and *M. oleifera* (Singo) in a doxorubicin-induced cardiotoxicity mouse model, assessing cardiac function and inflammatory markers simultaneously. The study measured cardiac functional parameters including ejection fraction, radial strain, and longitudinal strain, while also detecting myocardial NLRP3, NF- κ B, and 13 cytokine levels. Singo significantly improved ejection fraction and fractional shortening and reduced myocardial NLRP3, NF- κ B, and pro-inflammatory cytokine levels ($p < 0.05$). However, because the intervention was a three-component combination, the effects cannot be attributed to *M. oleifera* alone.

5.5.2 Clinical evidence: hs-CRP and HbA1c in diabetic patients

Mozo & Caoile-Ang (2015) conducted a prospective cohort study enrolling 56 diabetic patients who received *M. oleifera* leaf capsule supplements for 12 weeks, with simultaneous measurement of high-sensitivity C-reactive protein (hs-CRP, a cardiovascular risk marker) and glycated haemoglobin (HbA1c, a glycaemic control index). Results showed that hs-CRP decreased from a baseline of 3.38 mg L⁻¹ to 1.69 mg L⁻¹ ($p < 0.0001$), and HbA1c decreased from 6.96% to 6.06%, a mean reduction of 0.6% ($p < 0.0001$). This study captured changes across two dimensions, cardiovascular inflammatory risk and metabolic control—but did not directly measure immune cell function or cytokine profiles.

5.5.3 Preclinical evidence: T cell signalling in spontaneously hypertensive rats

Attakpa et al. (2017) evaluated the effects of a diet enriched with *M. oleifera* extract on blood pressure and T cell function in spontaneously hypertensive rats (SHR). Results showed that the *M. oleifera* diet lowered blood pressure in SHR while inhibiting anti-CD3-stimulated T cell proliferation and reducing IL-2 secretion in SHR (but not in normotensive WKY rats). This study simultaneously measured a cardiovascular endpoint (blood pressure) and immune endpoints (T cell proliferation, IL-2), making it one of the few preclinical studies to directly assess cardiovascular-immune interaction.

5.5.4 Evidence limitations and conclusion

These studies have clear limitations. First, combination-formulation studies cannot isolate the independent contribution of *M. oleifera*. Second, the clinical study had a small sample size ($n = 56$), a non-randomised design, lacked a placebo control, and did not report cytokine or immune cell subset data. Third, it remains unclear whether the immunomodulatory effects observed in animal models can be extrapolated to humans.

No well-designed randomised controlled trial has yet used cardiovascular events or immune-related clinical endpoints as primary outcomes while simultaneously assessing the dual effects of *M. oleifera* on the cardiovascular and immune systems. Therefore, the "dual targeting" potential of *M. oleifera* for cardiovascular-immune comorbidity remains at the level of mechanistic hypothesis rather than proven clinical effect.

Table 2 summarises the immunomodulatory mechanisms of *M. oleifera* across four mechanistic categories. Cytokine modulation is the most extensively documented, with MIC-1 suppressing TNF- α , IL-1 β , and IL-6 and inhibiting iNOS and COX-2 in LPS-stimulated mouse myoblasts (Jaja-Chimedza et al., 2022), while Nrf2/Keap1 activation and NF- κ B co-regulation have been demonstrated in murine sepsis models (Sailaja et al., 2021).

Immune cell regulation evidence derives largely from human HIV populations, where CD4⁺ and CD8⁺ T lymphocyte proliferation and IL-10 promotion have been reported (Sianipar et al., 2026; Waruguru et al., 2022). Murine studies support polysaccharide-mediated effects, including gut microbiota modulation and arabinogalactan-mediated immune activation (Mohai Ud Din et al., 2025). Notably, most mechanistic evidence is preclinical, and the species/model column reveals that human data are confined to HIV cohorts.

Table 2. Immunomodulatory mechanisms of *Moringa oleifera*: mediators, experimental models, and evidence sources.

Mechanism	Effect	Key Mediators	Species / Model	Reference
Cytokine modulation	Suppression of pro-inflammatory cytokines	TNF- α , IL-1 β , IL-6	Mouse myoblasts (C2C12); LPS-induced inflammation	Jaja-Chimedza et al. (2022)
	Suppression of pro-inflammatory cytokines	TNF- α , IL-1 β	Mouse model; LPS-induced sepsis	Sailaja et al. (2021)
	Inhibition of pro-inflammatory enzymes	iNOS, COX-2	Mouse myoblasts; LPS-induced inflammation	Jaja-Chimedza et al. (2022)
	Inhibition of prostaglandin synthesis	PGE ₂ (product of COX-2/mPGES-1)	Mouse myoblasts; LPS-induced inflammation	Jaja-Chimedza et al. (2022)
	Promotion of anti-inflammatory cytokines	IL-10	Human clinical studies (HIV populations)	Sianipar et al. (2026)
	Activation of PPAR- γ	Enhanced anti-inflammatory mediator production	Mouse myoblasts; LPS-induced inflammation	Jaja-Chimedza et al. (2022)
	T lymphocyte proliferation	CD4 ⁺ , CD8 ⁺ T cells	Human clinical studies (HIV populations)	Sianipar et al. (2026)
Immune regulation	cell NK cell cytotoxicity enhancement	Natural killer cells	Mouse model; leaf ethanol extract	Tilaoui et al. (2025)
	Treg polarisation reduction	Regulatory T cells	Tumour microenvironment (preclinical)	Tilaoui et al. (2025)

Polysaccharide-mediated	Gut microbiota modulation	<i>Muribaculaceae, Lactobacillus</i>	Mouse model; arabinogalactan administration	Mohai Ud Din et al. (2025)
	Arabinogalactan immunomodulation	Gut-associated immune system activation	Mouse model; MOLP-PE polysaccharide	Mohai Ud Din et al. (2025)
	Anti-inflammatory cytokine promotion	IL-10	Mouse model; polysaccharide fraction	Mohai Ud Din et al. (2025)
	Pro-inflammatory enzyme inhibition	COX-2	Mouse model; polysaccharide fraction	Mohai Ud Din et al. (2025)
Antioxidant-immune axis	Endogenous antioxidant enhancement	Nrf2/Keap1 pathway activation	Mouse model; MIC-1 administration	Sailaja et al. (2021)
	ROS neutralization	Reactive oxygen species	Mouse myoblasts; MIC-1	Jaja-Chimedza et al. (2022)
	Oxidative stress reduction	NF-κB and Nrf2 co-regulation	Mouse model; LPS-induced sepsis	Sailaja et al. (2021)

Note: Abbreviations: COX-2, cyclooxygenase-2; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MIC-1, moringa isothiocyanate-1; NK, natural killer; Nrf2, nuclear factor erythroid 2-related factor 2; PGE₂, prostaglandin E₂; PPAR-γ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; TNF-α, tumour necrosis factor alpha; Treg, regulatory T cell. Source: Authors, 2026.

Figure 5 illustrates the hierarchical cascade through which *M. oleifera* bioactive compounds exert their immunomodulatory effects. The plant's phytochemicals, including flavonoids (quercetin, kaempferol), isothiocyanates (moringin), and polysaccharides (arabinogalactans), target three major classes of molecular effectors. First, pro-inflammatory cytokines such as TNF-α and IL-1β are suppressed, alongside inhibition of pro-inflammatory enzymes including iNOS, COX-2, and PGE-2.

Second, the transcription factor PPAR-γ is activated, enhancing anti-inflammatory mediator production. Third, anti-inflammatory cytokines, particularly IL-10, are promoted. These converging pathways culminate in reduced inflammation, diminished oxidative stress, and enhanced overall immune function. This mechanistic architecture is consistent with reports that *M. oleifera* modulates inflammation by suppressing NF-κB and enhancing Nrf2/Keap1 antioxidant pathways.

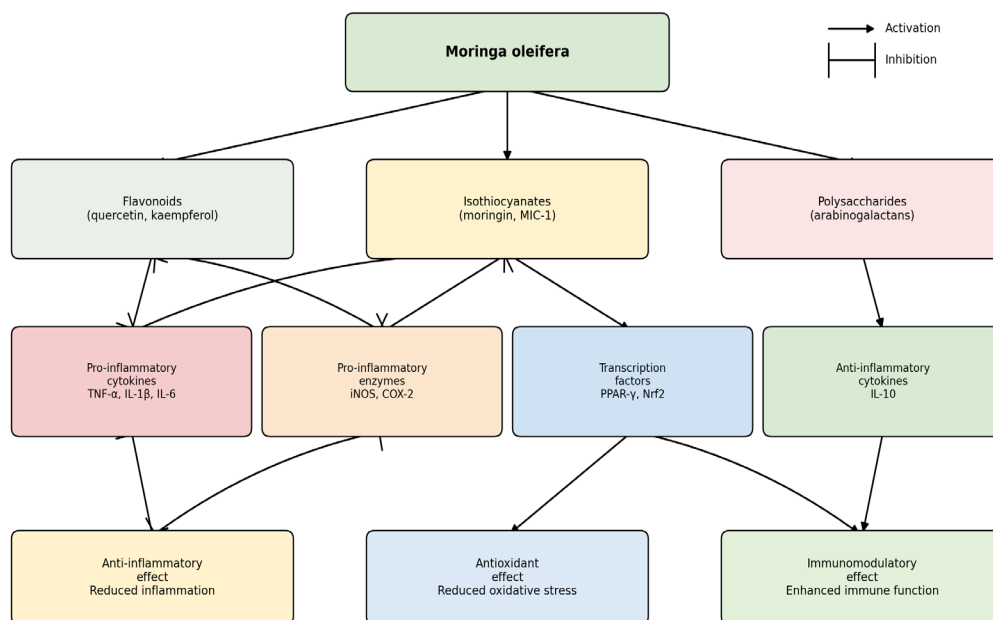


Figure 5. Molecular mechanisms of *Moringa oleifera* immunomodulation: suppression of pro-inflammatory cytokines (TNF- α , IL-1 β), inhibition of iNOS/COX-2, promotion of IL-10, and activation of PPAR- γ . Source: Authors, 2026.

4.8 Immune cell regulation

Figure 6 depicts the regulatory effects of *M. oleifera* on key immune cell populations and the gut microbiome. The plant enhances the proliferation and clonal expansion of CD4⁺ and CD8⁺ T lymphocytes while simultaneously augmenting natural killer (NK) cell cytotoxicity. Concurrently, *M. oleifera* modulates regulatory T cell (Treg) polarisation within the tumour microenvironment. A distinct mechanism involves gut-associated immune system activation through beneficial modulation of gut microbiota composition, notably increasing genera such as *Muribaculaceae* and *Lactobacillus*. These coordinated actions, enhanced T cell response, increased NK cell activity, reduced Treg polarisation, and favourable microbiota shifts, collectively strengthen host immune surveillance and defence

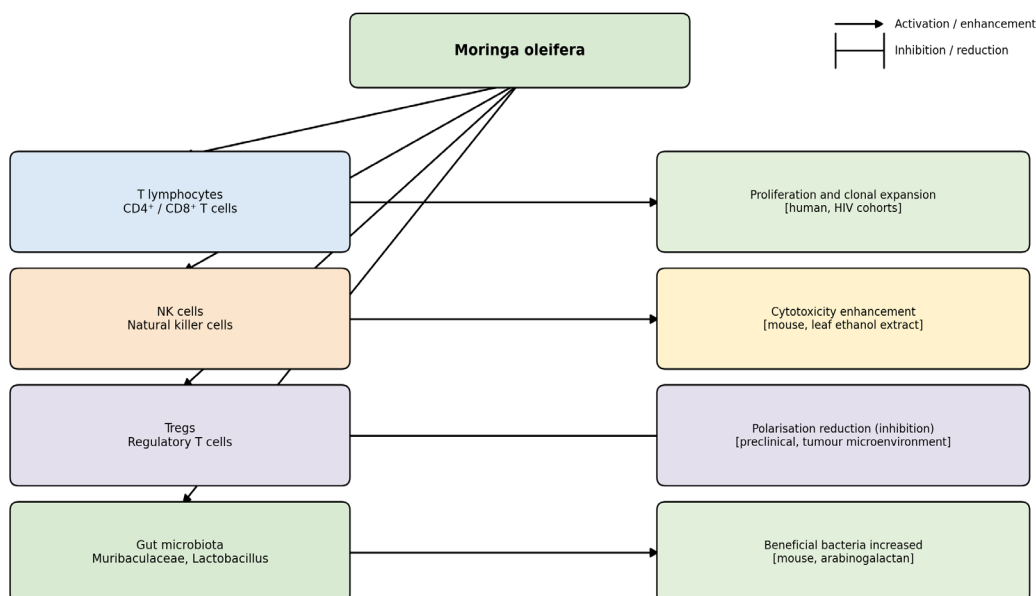


Figure 6. *Moringa oleifera* immune cell regulation: enhancement of CD4⁺/CD8⁺ T cell proliferation, NK cell cytotoxicity, modulation of Treg polarization, and gut microbiota modulation (*Muribaculaceae*, *Lactobacillus*). Source: Authors, 2026.

6. Clinical Evidence, Critical Appraisal, and Translational Gaps

6.1 Summary of clinical evidence

The clinical evidence base for *M. oleifera* supplementation presents a complex and discordant picture, with outcomes varying considerably across health domains. The most comprehensive synthesis to date, a meta-analysis of nine randomised controlled trials (RCTs) comprising 12 study arms and 649 participants (341 intervention, 308 control), evaluated the impact of *M. oleifera* supplementation on cardiometabolic outcomes (Crişan et al., 2025). The findings revealed no significant effects on most considered outcomes.

A modest reduction in diastolic blood pressure was observed (standardised mean difference [SMD]: -0.41; 95% confidence interval [CI]: -0.75 to -0.07; $p = 0.02$; $I^2 = 19\%$); however, this effect was not robust in sensitivity analyses, and the certainty of evidence was graded as very low for all evaluated outcomes (Crişan et al., 2025). Subgroup analyses suggested potential benefits at doses below 10 g day⁻¹, in participants under 50 years of age, and in interventions lasting 12 weeks or longer (Crişan et al., 2025).

Blood pressure evidence remains mixed. Afiaenyi et al. (2025) conducted a parallel-group RCT in 40 type 2 diabetic subjects in rural Nigeria, randomised to control, or 20, 40, or 60 g day⁻¹ fresh *M. oleifera* leaves for 14 days. Group 3 (40 g day⁻¹) showed a within-group reduction in systolic blood pressure (from 136.40 ± 7.66 to 123.90 ± 13.82 mmHg; $p = 0.01$) (Afiaenyi et al., 2025). However, after adjusting for pre-intervention values, there was no significant between-group difference in any parameter ($p > 0.05$), and Group 3 also showed a significant increase in triglycerides (from 123.80 ± 53.69 to 151.20 ± 41.47 mg dL⁻¹; $p = 0.04$) (Afiaenyi et al., 2025). The authors concluded that improvements were marginal and not dose-dependent (Afiaenyi et al., 2025).

A systematic review of the clinical antihypertensive efficacy and safety of *M. oleifera* leaf identified 16 studies, of which only one was a randomised placebo-controlled blinded trial; the remainder were non-randomised open-label or single-group designs (Adegoke et al., 2025). The review concluded that while limited literature suggests *M. oleifera* leaf supplementation may lower blood pressure in hypertensive persons, methodological deficiencies limit confidence in these findings (Adegoke et al., 2025).

The clinical evidence for *M. oleifera* is characterised by substantial heterogeneity in preparations, doses, durations, and populations. The Crişan et al. (2025) meta-analysis reported I^2 values frequently exceeding 80% for anthropometric and lipid parameters, precluding definitive conclusions. The certainty of evidence was rated very low using GRADE, reflecting serious concerns regarding risk of bias, inconsistency, indirectness, and imprecision (Crişan et al., 2025). In contrast, immune function in HIV populations presents a more consistent positive evidence base.

A systematic review and meta-analysis of seven articles (eight study datasets) demonstrated that *M. oleifera* supplementation significantly increased CD4⁺ T cell count (SMD = 1.4, 95% CI 0.59–2.20, $p < 0.001$), white blood cell count (SMD = 0.22, 95% CI 0.02–0.42, $p = 0.030$), and platelet count (SMD = 3.14, 95% CI 2.37–3.92, $p < 0.001$), with significant improvement in body mass index (SMD = 0.29, 95% CI 0.03–0.55, $p = 0.028$) (Tessema et al., 2025). However, even these findings derive from studies with methodological limitations, including small sample sizes and short intervention durations (Sianipar et al., 2026; Tessema et al., 2025).

Lipid profile modulation has yielded inconsistent results across studies. Some evidence suggests potential for HDL cholesterol enhancement, but findings are not uniformly replicated (Crişan et al., 2025). The meta-analysis reported substantial heterogeneity (I^2 frequently exceeding 80%) for lipid parameters, precluding definitive conclusions (Crişan et al., 2025). Glycemic control evidence suggests potential improvements in glycaemic parameters, though findings require confirmation through larger, well-designed trials (Sianipar et al., 2026; Pareek et al., 2024).

6.2 Critical appraisal of evidence quality

The quality of evidence supporting *M. oleifera*'s clinical efficacy is critically limited by multiple factors. Risk of bias assessment using the Cochrane RoB 2 tool revealed substantial methodological concerns across included RCTs (Crişan et al., 2025). Substantial heterogeneity (I^2 frequently exceeding 80% for anthropometric and lipid

parameters) indicates considerable variability in study populations, interventions, and outcomes that undermines the reliability of pooled estimates (Crişan et al., 2025).

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) assessment concluded that the certainty of evidence was very low for all evaluated cardiometabolic outcomes. This rating reflects serious concerns regarding risk of bias, inconsistency, indirectness, and imprecision of effect estimates (Crişan et al., 2025).

Methodological limitations are pervasive across the clinical literature. Common deficiencies include small sample sizes that lack statistical power to detect meaningful differences, lack of standardisation in interventions (varying plant parts, extraction methods, dosages, and formulations), and short intervention durations that may be insufficient to observe clinically meaningful changes in chronic disease markers (Crişan et al., 2025; Sianipar et al., 2026).

Study design issues compound these limitations. Many trials exhibit inadequate randomization procedures, lack of blinding (increasing risk of performance and detection bias), and high attrition rates that compromise the validity of findings (Crişan et al., 2025). The variability in interventions, including different plant parts (leaves, seeds, roots), extraction methods (aqueous, ethanolic, powdered), dosages (ranging widely from <1 g to >20 g day⁻¹), and formulations, creates substantial challenges for evidence synthesis and clinical translation (Pareek et al., 2024).

5.3 Safety and toxicity profile

General tolerability of *M. oleifera* leaf and seed preparations appears favourable. In general, *M. oleifera* is well tolerated when administered orally or topically at recommended doses (Sianipar et al., 2026). Common side effects are typically mild and transient, with gastrointestinal upset, including transient diarrhoea, reported in some studies (Clinical antihypertensive efficacy and safety, 2025). A systematic review of clinical antihypertensive efficacy reported no incidence of adverse events in two articles (n = 209), while others noted minor gastrointestinal upset and changes in appetite and sleep patterns (Clinical antihypertensive efficacy and safety, 2025).

Toxicity concerns at high doses warrant attention. Glucosinolates and tannins present in *M. oleifera* have been associated with potential hepatotoxicity, nephrotoxicity, and reproductive toxicity at elevated doses (Pareek et al., 2024). The roots and bark contain potentially toxic alkaloids, including spirochin and ephedrine-like stimulants, necessitating caution in their medicinal use (Alidadi et al., 2023; Pareek et al., 2024).

Rare adverse events have been reported, including hypersensitivity reactions and thrombotic events (Sianipar et al., 2026). Case reports exist of toxic reactions following consumption of moringa powder, including one report of Stevens-Johnson syndrome and one of cutaneous toxicity with respiratory distress and tongue oedema (Drugs.com, 2026). While these events are rare, they underscore the importance of careful monitoring and quality control in *M. oleifera* supplementation.

6.4 Key translational gaps

Several critical gaps impede the translation of preclinical promise into evidence-based clinical application. The disconnect between preclinical and clinical efficacy represents the most fundamental translational challenge. While robust mechanistic evidence from *in vitro* and *in vivo* studies consistently demonstrates cardioprotective and immunomodulatory effects, these findings have not consistently translated to human trials (Crişan et al., 2025; Mehta et al., 2026). This discordance may reflect differences in bioavailability, dosing, study design, and outcome selection between preclinical and clinical investigations.

The lack of standardised formulations represents a major obstacle to clinical translation. Variability in bioactive compound profiles across commercially available products, coupled with inconsistent extraction and processing methods, makes it difficult to compare findings across studies or establish reliable dose-response relationships (Pareek et al., 2024; Sianipar et al., 2026).

Dose optimisation remains unclear. While subgroup analyses suggest potential benefits at doses below 10 g day⁻¹, the optimal dosing parameters, including frequency, duration, and formulation, have not been established (Crişan et al., 2025).

Bioavailability limitations constrain the therapeutic potential of key polyphenolic compounds. Poor gastrointestinal absorption, limited skin permeability, and efflux transport mechanisms restrict systemic

exposure to many bioactive constituents (Alidadi et al., 2023). Novel formulation techniques, including nanoformulation and lipid-based delivery systems, are being explored to address these limitations (Mehta et al., 2026).

Long-term safety data are insufficient to support recommendations for chronic use. Most clinical trials have been of short duration (typically 2–12 weeks), and the safety profile of prolonged *M. oleifera* supplementation remains inadequately characterised (Crişan et al., 2025; Sianipar et al., 2026).

Drug interaction potential is a significant concern, particularly given the widespread use of *M. oleifera* as a complementary therapy in populations already receiving conventional medications. Studies have demonstrated pharmacokinetic interactions between *M. oleifera* leaf powder and amodiaquine in healthy human volunteers, suggesting potential for herb-drug interactions (*M. oleifera* leaf powder alters the pharmacokinetics of amodiaquine, 2018). Limited data exist on interactions with other commonly used medications, including antiretroviral, antihypertensive, and antidiabetic agents.

Population-specific effects may exist, with subgroup analyses suggesting potential benefits in specific populations, including individuals less than 50 years of age, those receiving doses below 10 g day⁻¹, and interventions lasting 12 weeks or longer (Crişan et al., 2025). However, these findings require confirmation through adequately powered studies.

7. Conclusion

Moringa oleifera possesses a rich and diverse phytochemical arsenal with demonstrated cardioprotective and immunomodulatory activities through multiple molecular pathways, including NF- κ B inhibition, Nrf2/Keap1 activation, PI3K/Akt modulation, AMPK activation, PPAR modulation, and MAPK pathway attenuation. The mechanistic evidence, particularly the suppression of pro-inflammatory cytokines (TNF- α , IL-1 β), inhibition of pro-inflammatory enzymes (iNOS, COX-2) and prostaglandin PGE₂, promotion of anti-inflammatory cytokines (IL-10), and activation of PPAR- γ , is consistent across preclinical studies.

However, this evidence derives predominantly from in vitro and rodent models, and the plasma concentrations achievable in humans for most constituents remain undetermined. Consequently, these mechanisms should be regarded as biologically plausible rather than clinically established.

A critical evidence gap exists: rigorous clinical translation has not kept pace with preclinical promise. Current evidence does not support consistent cardiometabolic benefits of *M. oleifera* supplementation in adults, and the certainty of evidence for all evaluated cardiometabolic outcomes is very low (Crişan et al., 2025). The modest, non-robust reduction in diastolic blood pressure reported in the meta-analysis does not justify therapeutic recommendations. While more consistent positive evidence exists for immune function, particularly in populations living with HIV, methodological limitations including small sample sizes, lack of standardisation, short intervention durations, and high risk of bias undermine confidence in these findings (Sianipar et al., 2026; Tessema et al., 2025).

The path forward requires a coordinated, multi-priority research agenda encompassing: (1) high-quality randomised controlled trials with standardised preparations and clinically meaningful endpoints; (2) biomarker-driven mechanistic validation in humans; (3) bioavailability-enhancing nanoformulation strategies; (4) robust standardisation and quality control frameworks; (5) long-term safety surveillance and pharmacovigilance, including drug-interaction studies; (6) systems biology and multi-omics approaches to elucidate polypharmacological mechanisms; and (7) translation of evidence into clinical practice guidelines, supported by cost-effectiveness analyses in resource-limited settings.

With strategic research investment, cross-sector collaboration, and supportive policies, *M. oleifera* holds genuine potential as a safe, accessible, and sustainable adjunctive therapeutic agent, particularly in resource-limited settings where chronic disease burdens are highest. Until such evidence accrues, *M. oleifera* should be viewed as a supportive supplement, not a primary treatment, and its use should be guided by emerging evidence and careful clinical judgment.

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7. Authors' Contributions

Belay Sitotaw Goshu: conceived and designed the review, conducted the literature search and critical appraisal, and drafted the manuscript. *Melaku Masresha Woldeamanuel*: contributed to the formulation of the review framework and revised the manuscript critically. Both authors read and approved the final manuscript.

8. Conflicts of Interest

No conflicts of interest.

9. Ethics Approval

Not applicable. This review did not involve human or animal subjects.

10. Artificial Intelligence Statement: Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that generative artificial intelligence (AI) tools were used in the preparation of this manuscript for grammatical corrections and language editing in both English and Portuguese, as well as for the creation of the graphical abstract. All AI-assisted content was reviewed, verified, and approved by the authors, who assume full responsibility for the accuracy, integrity, and scientific content of the manuscript. The use of AI in the graphical abstract is disclosed in its caption, including the name of the tool. AI tools are not authors and cannot assume authorship or responsibility for the content of the manuscript.

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