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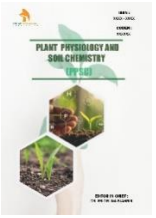

RESEARCH ARTICLE

PHYTOCHEMICAL DIVERSITY AND PHARMACOLOGICAL POTENTIAL OF THE GENUS MORINGA: A CRITICAL REVIEW OF SPECIALIZED METABOLITES AND THERAPEUTIC INSIGHTS

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ABSTRACT

The genus Moringa (family Moringaceae), comprising 13 species distributed across Africa, the Indian subcontinent, and the Arabian Peninsula, represents a phytochemically rich and pharmacologically significant group of plants. Among these, Moringa oleifera, M. stenopetala, and M. peregrina have been most extensively investigated for their diverse array of bioactive compounds. This review presents a critical synthesis of specialized metabolites, including glucosinolates, flavonoids, phenolic acids, alkaloids, and isothiocyanates, with emphasis on their biosynthetic pathways, structural characteristics, and chemotaxonomic relevance. The pharmacological spectrum of these compounds is discussed in detail, covering antioxidant, anti-inflammatory, anticancer, neuroprotective, and antimicrobial activities, alongside mechanistic insights and molecular targets. Key research gaps are highlighted, particularly the underrepresentation of lesser-known Moringa species and the limited translational and in vivo validation of reported bioactivities. The review advocates for integrative methodologies such as metabolomics, transcriptomics, and bioassay-guided compound isolation to enhance species-specific characterization and therapeutic exploration. By consolidating current findings and proposing future research directions, this review aims to advance the scientific understanding of Moringa phytochemistry and pharmacology, and to facilitate the development of novel therapeutic agents from this underutilized genus.

KEYWORDS

Bioprospecting, Chemotaxonomy, Flavonoids, Glucosinolates, Moringa, Pharmacological activity, Specialized metabolites.

1. INTRODUCTION

The genus Moringa, belonging to the family Moringaceae also known as the "drumstick" or "horseradish" family shares this taxonomic group with the genera Anoma and Hyperanthera. The Moringa genus encompasses 13 recognized species that are distributed across regions including Southwest Asia, Northeast and Southwest Africa, and Madagascar. Among the 13 recognized Moringa species, current research efforts have predominantly focused on Moringa oleifera, Moringa stenopetala, Moringa concanensis, and Moringa peregrina. The remaining species, which are largely endemic to Madagascar and Northeast Africa, have received comparatively limited scientific attention, primarily due to reduced bioprospecting activities and minimal exploration of their phytochemical profiles in these regions. In contrast, M. oleifera, native to India, has garnered extensive global interest owing to its well-documented nutritional and pharmacological properties. Consequently, it has been widely cultivated across diverse geographical regions, particularly in Asia, Latin America, Florida, and the Caribbean (Fahey, 2005). The species within the Moringa genus can be taxonomically categorized into three distinct groups based on trunk morphology (Olson and Rosell, 2006). Moringa stenopetala, M. drouhardii, M. ovalifolia, and M. hildebrandtii are characterized by their swollen, water-storing trunks and are commonly referred to as "bottle trees." In contrast, species such as M. peregrina, M. concanensis, and M. oleifera possess slender, non-swollen trunks. The remaining species, which are predominantly endemic to Northeast Africa, exist as tuberous shrubs. Notably, Moringa species exhibit remarkable drought tolerance and are capable of rapid growth with minimal agronomic input. The Moringa genus has long been utilized in traditional medicine for its health-promoting properties. Historical accounts suggest that royalty, including kings and queens, consumed Moringa to enhance mental alertness and maintain healthy skin. In ancient India, Moringa oleifera leaves were administered to warriors to boost physical stamina, alleviate pain, and reduce stress during times of war (Mahmood et al., 2010). Other traditional applications of the Moringa genus include the treatment of various ailments such as skin infections, anxiety, asthma, wounds, fever, diarrhea, and sore throats. The Moringa genus is renowned for its multifaceted applications. The seeds are utilized for water purification, the leaves serve as nutritional supplements, the oil is employed as a biofuel, the trunks are a source of gum, and the flowers contribute to honey production. Additionally, nearly all parts of the plant possess medicinal value and are widely used in traditional and contemporary therapeutic practices (Fahey, 2005). Moringa oleifera, commonly referred to as the “Miracle Tree” and “Mother’s Best Friend,” is widely recognized as one of the most nutrient-dense plants known. In addition to its remarkably high content of vitamins A and C, potassium, and calcium, M. oleifera also provides all essential amino acids, making it a complete plant-based source of vital nutrients (Mahmood, K. T., Mugal and Haq, 2010). Extensive research has been conducted on the Moringa genus to investigate its diverse biological properties, with Moringa oleifera receiving particular attention since the 1970s (Mahmood et al.,

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2010). At present, Moringa oleifera is well-documented for its potent anti-inflammatory, antioxidant, anticancer, and antidiabetic activities. In recent years, research interest has begun to extend to other species within the genus, including M. concanensis, M. stenopetala, and M. peregrina. However, comprehensive scientific investigations on the remaining species are still lacking. This review aims to consolidate existing knowledge on the traditional uses, phytochemical composition, and biological activities of the Moringa genus, with the goal of promoting future research on the lesser-studied species.

2. Phytochemical Landscape Of Moringa Species

2.1 Glucosinolates and Isothiocyanates

Moringa species are rich in glucosinolates, with the most abundant being 4-O-α-L-rhamnopyranosyloxy-benzyl glucosinolate, commonly known as glucomoringin or GMG. Additionally, three isomers of 4-O-α-L-acetylrhamnopyrosyloxy-benzyl glucosinolate have been identified in Moringa oleifera leaves, with their presence varying based on the maturity and physiological characteristics of the leaves (Leone, A., Spada, A., Battezzati, A., Schiraldi, A., Aristil, J., and Bertoli, S. 2015b). Disruption of plant tissues, typically through cutting or chewing, triggers the release of the enzyme myrosinase. When myrosinase comes into contact with glucosinolates, it catalyzes their hydrolysis, leading to the formation of bioactive compounds such as isothiocyanates. The most abundant isothiocyanate identified in the Moringa genus is 4-α-L-rhamnosyloxy-benzyl isothiocyanate, also known as GMG-ITC, which is derived from the hydrolysis of 4-O-α-L-rhamnopyranosyloxy-benzyl glucosinolate, commonly referred to as glucomoringin. In recent years, isothiocyanates have garnered significant scientific interest due to their wide range of biological activities, including anticancer, antidiabetic, antimicrobial, and anti-inflammatory effects (Park et al., 2011; Waterman et al., 2015). The biological activity of isothiocyanates is largely attributed to their ability to undergo alkylation reactions with proteins and DNA (Nibret and Wink, 2010). An in vitro callus culture study was conducted on Moringa peregrina to induce isothiocyanate production; however, the attempt was unsuccessful in generating any isothiocyanates (Dehshahri et al., 2012a). Isothiocyanates are typically found in nature as volatile oils, characterized by their instability at room temperature. This inherent volatility and thermal sensitivity often limit their practical applications and shelf life. However, the isothiocyanate derived from Moringa oleifera exhibits a remarkable exception to this norm. Unlike typical isothiocyanates, M. oleifera's isothiocyanate is highly stable and exists in a solid form at room temperature. This enhanced stability is primarily attributed to the presence of an additional sugar moiety specifically, an α-L-rhamnose group attached to its molecular structure. The glycosylation not only increases the molecular weight but also improves its solubility and reduces volatility, thereby contributing to its solid state and thermal resilience. This unique structural feature significantly enhances the pharmacological utility of M. oleifera's isothiocyanate, making it more suitable for therapeutic and industrial applications (Tumer et al., 2015).

2.2 Flavonoids

The Moringa genus is recognized for its potent antioxidant properties, primarily attributed to its rich concentration of flavonoid compounds. Within this genus, the predominant flavonoids are primarily found in the form of flavanols and glycosides. Among the most frequently identified flavonoids in Moringa species are rutin, quercetin, rhamnetin, kaempferol, apigenin, and myricetin. Extensive research has been undertaken to optimize the extraction process of flavonoids from Moringa oleifera, aiming to achieve the highest possible yield. Comparative studies evaluating various extraction methods have revealed that subcritical ethanol extraction is significantly more effective. Specifically, this method resulted in a 26.7% higher yield of flavonoids compared to the traditional reflux extraction technique (Wang et al., 2017).

2.3 Phenolic acids

The leaves of Moringa oleifera are rich in phenolic acids, with gallic acid identified as the predominant compound. In addition to gallic acid, several other phenolic acids such as ellagic acid, ferulic acid, caffeic acid, ortho-coumaric acid, and chlorogenic acid have been detected in appreciable amounts. Furthermore, a number of phenolic acids including gentisic acid, syringic acid, para-coumaric acid, and sinapic acid have also been identified, albeit in only trace concentrations. These phenolic compounds contribute significantly to the antioxidant and therapeutic properties of M. oleifera leaves (Leone et al. 2015a; Leone et al., 2015b). According to studies conducted the primary carotenoid identified in the leaves of Moringa oleifera is lutein by (Teixeira et al., 2014; Saini et al., 2014). This compound is known for its strong antioxidant properties and plays a crucial role in contributing to the nutritional and therapeutic value of the plant (Teixera et al., 2014; Saini eta la., 2014). As study reported that Moringa oleifera leaves do not contain α-carotene, a carotenoid commonly found in green leafy vegetables (Saini et al., 2014). The absence of α-carotene in M. oleifera was attributed to the possibility that it may have undergone complete metabolic conversion into lutein, a dominant carotenoid in the plant. In addition to lutein, several other carotenoids have been identified in M. oleifera leaves. These include all-E-luteoxanthin, 13-Z-lutein, 15-Z-β-carotene, and all-E-zeaxanthin. These compounds contribute to the plant's antioxidant capacity and enhance its potential health benefits, particularly in supporting eye health and reducing oxidative stress (Teixera et al., 2014). Lupeol acetate, β-amyrin, and α-amyrin have been successfully isolated from the n-hexane fraction of an ethanol extract derived from the aerial parts of Moringa peregrina. These compounds are classified as pentacyclic triterpenoids, a group of naturally occurring bioactive molecules known for their wide range of pharmacological activities. The extraction process involved the use of ethanol to obtain a crude extract from the plant's aerial parts, which was then subjected to further fractionation using n-hexane to separate non-polar constituents. Lupeol acetate is a derivative of lupeol, a compound well-documented for its anti-inflammatory, anticancer, and antimicrobial properties. β-Amyrin and α-amyrin are structural isomers, both possessing notable anti-inflammatory, hepatoprotective, and analgesic activities. The presence of these triterpenoids in M. peregrina highlights the therapeutic potential of the plant and supports its traditional use in herbal medicine. Their isolation from the n-hexane fraction suggests that these compounds are predominantly lipophilic in nature, aligning with their structural characteristics (El-Alfy et al., 2011).

2.4 Alkaloids

Two novel pyrrole alkaloid glycosides, named marumoside A and marumoside B, were isolated from the leaves of Moringa oleifera. These compounds represent a unique class of naturally occurring nitrogen-containing secondary metabolites characterized by a pyrrole ring structure conjugated with sugar moieties. In addition to marumoside A and B, another related compound, pyrrolemarumine-4''-O-α-L-rhamnopyranoside, was also identified from the same plant extract. The isolation of these alkaloid glycosides involved careful extraction and purification processes, typically using solvent extraction followed by chromatographic techniques such as column chromatography and high-performance liquid chromatography (HPLC). Structurally, marumoside A and marumoside B consist of a pyrrole nucleus attached to glycosidic chains, contributing to their solubility and potential biological activity. These pyrrole alkaloid glycosides are of significant interest due to their potential pharmacological properties, which may include antioxidant, anti-inflammatory, antimicrobial, or neuroprotective effects. The presence of the rhamnopyranoside sugar unit in pyrrolemarumine-4''-O-α-L-rhamnopyranoside further suggests enhanced bioavailability and transport within biological systems. The discovery of these novel compounds adds to the growing body of evidence supporting the therapeutic potential of M. oleifera and underscores the chemical diversity of its phytoconstituents (Sahakitpichan et al., 2011).

2.5 Sterols

A sterol glycoside identified as β-sitosterol-3-O-β-D-galactopyranoside was isolated from the chloroform extract of the stem bark of Moringa oleifera. This compound belongs to the class of phytosterols, which are plant-derived sterols structurally similar to cholesterol, and is conjugated with a galactose sugar moiety. The isolation highlights the presence of bioactive sterol glycosides in the stem bark, contributing to the pharmacological potential of the plant (Bargah and Das, 2014). The oil extracted from Moringa peregrina has been found to contain a significant proportion of steroidal components, which are primarily phytosterols known for their health-promoting properties. The predominant sterol identified in the oil is β-sitosterol, which constitutes approximately 56.76% of the total sterol content. β-Sitosterol is a well-known bioactive compound that exhibits cholesterol-lowering, anti-inflammatory, and anticancer properties. The second most abundant component is campesterol, accounting for 23.24% of the sterol fraction. Campesterol, structurally similar to cholesterol, contributes to cardiovascular health by competing with cholesterol absorption in the intestines. Stigmasterol is the third major steroidal constituent, comprising 8.11% of the sterol content. This compound is recognized for its antioxidant, anti-inflammatory, and hypoglycemic effects. The presence of these phytosterols in M. peregrina oil not only enhances its nutritional value but also underlines its potential use in functional foods, nutraceutical formulations, and traditional medicine for promoting cardiovascular and metabolic health (Abd El Baky and El-Baroty, 2013). β-Sitosterol, a prominent phytosterol, has been successfully isolated from both the leaves and seeds of Moringa oleifera. This plant-derived sterol shares a structural resemblance to cholesterol but differs by possessing an extra ethyl group at the C-24 position, which imparts unique biological functions. In M.

oleifera, β-sitosterol represents one of the key bioactive compounds contributing to the plant's wide range of therapeutic applications. Its isolation typically involves organic solvent extraction—commonly using ethanol, methanol, or chloroform—followed by chromatographic purification techniques such as column chromatography or thin-layer chromatography (TLC). Biologically, β-sitosterol is well-documented for its hypocholesterolemic activity, as it competes with dietary cholesterol for absorption in the intestinal tract, thereby reducing blood cholesterol levels. In addition, it exhibits anti-inflammatory, antioxidant, immunomodulatory, and anticancer activities. The occurrence of β-sitosterol in both the vegetative (leaves) and reproductive (seeds) parts of M. oleifera highlights the plant's rich phytochemical profile and reinforces its value in traditional medicine and functional food applications (Maiyo et al., 2016). An acetone extract derived from the root wood of Moringa stenopetala has been reported to contain cholest-5-en-3-ol, a compound also known as cholesterol, which is a fundamental sterol in animal systems but occasionally found in plants in trace amounts. Its presence in M. stenopetala is particularly noteworthy, as it suggests the occurrence of uncommon sterol biosynthesis pathways in this species of the Moringa genus. Cholest-5-en-3-ol possesses a cyclopentanoperhydrophenanthrene ring system with a double bond between the 5th and 6th carbon atoms and a hydroxyl group at the 3rd carbon position. In the context of phytochemistry, this compound may arise as an intermediate or byproduct in the biosynthetic conversion of plant sterols. The extraction with acetone a polar organic solvent facilitates the isolation of a broad range of semi-polar compounds, including sterols and triterpenoids. The identification of cholest-5-en-3-ol in M. stenopetala root wood adds to the growing understanding of the plant's chemical diversity and may open up avenues for exploring its biological functions, which could include membrane structural integrity and potential roles in plant defense mechanisms or bioactivity in pharmacological applications.

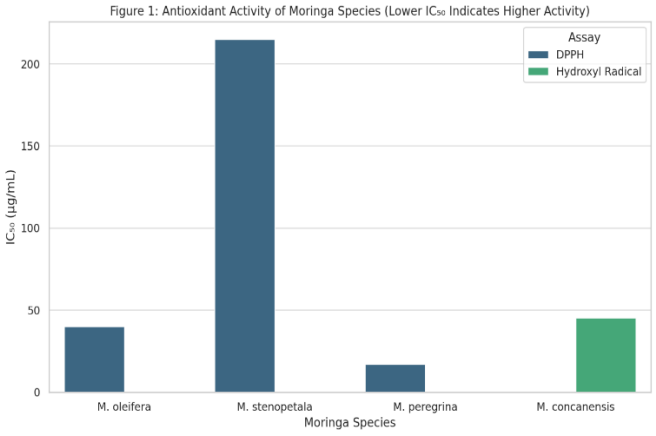
Table 1: Bioactive Sterols Identified in Moringa Species (Tesemma et al., 2013)

Compound	Moringa Species	Tissue	Concentration / Prevalence	Reference
β-Sitosterol	M. oleifera, M. peregrina	Leaves, Seeds, Oil	Up to 56.76% in oil (M. peregrina)	Abd El Baky and El-Baroty (2013)
Campesterol	M. peregrina	Seed oil	23.24% of sterol fraction	Abd El Baky and El-Baroty (2013)
Stigmasterol	M. peregrina	Seed oil	8.11%	Abd El Baky and El-Baroty (2013)
Cholest-5-en-3-ol	M. stenopetala	Root wood (acetone)	Detected	Tesemma et al. (2013)

3. Pharmacological Activities And Bio-Efficacy

3.1 Anti-oxidant and Anti-inflammatory Effects

The elevated phenolic content in Moringa species significantly contributes to their potent antioxidant properties. Phenolic compounds function as antioxidants by stabilizing free radicals within cells through electron donation or acceptance. Aqueous extracts of Moringa stenopetala leaves demonstrated greater free radical scavenging capacity, with a lower IC_{50} value (40 µg/mL) in the DPPH (1,1-diphenyl-2-picrylhydrazyl) assay, compared to Moringa oleifera leaf extracts (IC_{50}: 215 µg/mL). Notably, rutin (compound 1) exhibited exceptional antioxidant potential with an IC_{50} of 5 µg/mL. HPLC analysis further revealed that M. stenopetala contains a higher concentration of rutin, contributing to its superior antioxidant efficacy relative to M. oleifera (Habtemariam and Varghese, 2015). The methanolic fraction of Moringa peregrina leaves exhibited notable DPPH radical scavenging activity, with an IC_{50} value of 17.07 µg/mL, which was comparable to the antioxidant activity of ascorbic acid in the same assay (Al-Owaisi et al., 2014). HPLC analysis revealed that the hexane fraction of Moringa peregrina leaves lacked detectable phenolic compounds; however, it still demonstrated significant radical scavenging activity. It was reported that Moringa peregrina seed oil exhibited considerable antioxidant activity, comparable to that of conventional antioxidants such as BHA, α-tocopherol, and BHT (Abd El Baky and El-Baroty, 2013).Moringa ovalifolia, particularly its bark, contained quercetin, kaempferol, and myricetin, which exhibited antioxidant activity by enhancing ferric reducing capacity and inhibiting DPPH radical activity (Ananias, 2015). A study indicated that pre-treatment with Moringa peregrina leaves effectively prevented an increase in plasma hydrogen peroxide levels at doses of 200 and 400 mg/kg (Safaeian et al., 2015). At a dose of 400 mg/kg, it also significantly lowered elevated plasma hydrogen peroxide levels while enhancing ferric reducing antioxidant capacity. A methanolic extract of Moringa concanensis leaves exhibited strong antioxidant potential by inhibiting DPPH activity, hydroxyl radicals, reducing power, and superoxide anion radicals (Santhi and Sengottuvel, 2016). Notably, the extract demonstrated superior hydroxyl radical scavenging activity (IC_{50}: 45.3 µg/mL) compared to ascorbic acid (IC_{50}: 58.2 µg/mL) (Santhi and Sengottuvel, 2016). It was reported that the ethyl acetate fraction of a Moringa oleifera leaf hydromethanolic extract exhibited the highest activity. This fraction inhibited DPPH radicals with an IC_{50} of 0.04 mg/mL, which was comparable to the activity of quercetin, which showed DPPH inhibition at an IC_{50} of 0.02 mg/mL. Beyond in vitro assays, the ethyl acetate fraction was also evaluated in vivo using CCl_4-intoxicated rats (Verma et al., 2009), where it significantly increased the levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) (Verma et al., 2009). Pre-treatment with the hydroethanolic extract of Moringa oleifera leaves has been shown to effectively mitigate paracetamol-induced hepatotoxicity in Sprague-Dawley rats. This protective effect was evidenced by a significant reduction in lipid peroxidation levels, which are markers of oxidative damage to cell membranes. Additionally, the extract helped restore the balance of key antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), bringing their activities back toward normal levels. By decreasing oxidative stress and enhancing the liver's antioxidant defense system, the extract contributed to improved hepatic function and reduced tissue damage caused by paracetamol toxicity (Uma et al., 2010). A study was conducted to evaluate the effects of Moringa oleifera extract on fasting plasma glucose (FPG) levels and antioxidant status in healthy volunteers. The findings demonstrated that while the extract did not significantly alter FPG concentrations compared to the control group, which received only warm water, it markedly improved several markers of oxidative stress and antioxidant capacity. Specifically, plasma malondialdehyde (MDA) levels a biomarker of lipid peroxidation and oxidative damage were significantly reduced following extract administration. Concurrently, there was an increase in Trolox equivalent antioxidant capacity (TEAC), reflecting enhanced overall antioxidant potential. Additionally, the ferric reducing ability of plasma (FRAP), an indicator of the plasma's capacity to reduce oxidized intermediates, was significantly elevated. These results suggest that Moringa oleifera extract enhances systemic antioxidant defenses without affecting fasting blood glucose in healthy individuals (Ngamukote et al., 2016).



A study reported that the ethanolic extract of Moringa concanensis flowers and fruits exhibited anti-inflammatory effects, inhibiting inflammation by 78.4% and 44.08%, respectively (Rao et al., 2008; Jayabharathi and Chitra, 2011). An extract derived from the aerial parts of Moringa peregrina was found to alleviate peritoneal inflammation and significantly reduce the

permeability of small blood vessels (Elbatran et al., 2005). Ethanolic and aqueous extracts of Moringa peregrina seeds demonstrated inhibitory effects against acute inflammation induced by fresh egg albumin in rats, when administered orally at doses ranging from 100 to 300 mg/kg (Koheil et al., 2011).

The primary anti-inflammatory mechanism identified for Moringa oleifera involves the suppression of the NF-κB signaling pathway. Four different leaf fractions hexane, chloroform, ethyl acetate, and butanol—were shown to reduce the production of pro-inflammatory mediators including IL-1β, IL-6, PGE2, TNF-α, and nitric oxide in LPS-stimulated macrophages (Arulselvan et al., 2016). Among the tested fractions, the ethyl acetate extract exhibited the most potent anti-inflammatory activity and was subsequently subjected to further investigation. This extract effectively inhibited the nuclear translocation of NF-κB and enhanced the expression of inhibitor κB (IκB), a mechanism also observed in Moringa oleifera fruit extract. However, higher concentrations (500 and 1,000 µg/mL), particularly from the chloroform fraction, were found to be cytotoxic. It was reported that the ethyl acetate extract of Moringa oleifera leaves inhibited the expression of RelA (Kooltheat et al., 2014). A hydroethanolic extract of Moringa flowers was also shown to suppress the activity of inflammatory mediators and proinflammatory cytokines, including PGE2, IL-6, IL-1β, TNF-α, NF-κB, iNOS, nitric oxide (NO), and COX-2, in LPS-stimulated RAW264.7 macrophages (Tan et al., 2015). Additionally, the extract enhanced the levels of anti-inflammatory cytokines IL-10 and IκB-α. Among the various parts of Moringa oleifera, the fruit demonstrated the most significant effect in suppressing LPS-induced nitric oxide (NO) release in RAW264.7 cells (Lee et al., 2013). Aurantiamide acetate and 1,3-dibenzyl urea , isolated from Moringa oleifera roots, were found to inhibit IL-2 activity. Additionally, aurantiamide acetate demonstrated inhibitory effects on TNF-α activity (Sashidara et al., 2009). 4-α-L-rhamnosyloxybenzyl isothiocyanate and 4-4′-O-acetyl-α-L-rhamnosyloxybenzyl isothiocyanate isolated from Moringa oleifera leaves exhibited anti-inflammatory activity by modulating IL-1β and iNOS expression, as well as decreasing the production and expression of inflammatory markers in RAW macrophages (Waterman et al., 2014). The compound inhibited NF-κB activation, phosphorylation of ERK1/2, IκBα, and IKKα/β, while also promoting the degradation of IκBα. This isothiocyanate exhibited stronger activity compared to other isothiocyanates such as benzyl isothiocyanate and sulforaphane. Specifically, 4-α-L-rhamnosyloxybenzyl isothiocyanate, 4-2′-O-acetyl-α-L-rhamnosyloxybenzyl isothiocyanate, 4-3′-O-acetyl-α-L-rhamnosyloxybenzyl isothiocyanate, and 4-4′-O-acetyl-α-L-rhamnosyloxybenzyl isothiocyanate all inhibited nitric oxide production (Cheenpracha et al., 2010). The extract decreased the expression of mannose receptor mRNA, retinoic acid-related orphan receptor γT, and thymic stromal lymphopoietin in ear tissue. In vitro assays demonstrated that the extract suppressed mitogen-activated protein kinases, CCL17, IL-6 mRNA related to pro-inflammatory cytokines, as well as TNF-α and IL-1β expression. Additionally, Moringa oleifera pod extract inhibited the increase in protein and mRNA levels of cyclooxygenase-2, TNF-α, IL-6, and iNOS by blocking the phosphorylation of mitogen-activated protein kinases and NF-κB proteins (Muangnoi et al., 2012).

The immunosuppressive activity of the extract was demonstrated by its capacity to downregulate macrophage phagocytosis. The ethanolic seed extract also decreased white blood cell and leukocyte counts, which are typically involved in immune responses. However, it caused an increase in paw edema, a reaction commonly associated with type IV hypersensitivity. Meanwhile, methanolic extracts of Moringa oleifera leaves showed analgesic properties by alleviating mechanical allodynia and thermal hyperalgesia in rats with Freund's adjuvant-induced arthritis (Manaheji et al., 2011). The ethyl acetate fraction, derived from a hydroethanolic extract of Moringa oleifera leaves, promoted migration and proliferation of normal human dermal fibroblasts (Gothai et al., 2016). An aqueous fraction of Moringa oleifera leaves decreased scar size and accelerated wound closure, while also enhancing granuloma formation, skin tensile strength, granuloma dry weight, and hydroxyproline content in albino rats (Rathi et al., 2006). It was reported that a Moringa oleifera seed extract combined with Acacia arabica biopolymers showed potential as an effective wound dressing material. Besides exhibiting strong antimicrobial properties, these biopolymers were biodegradable and demonstrated water absorption capacities ranging from 415% to 935%. Additionally, they reduced the activation time of partial prothrombin and thromboplastin (Bhatnagar et al., 2013).

Table 2: Comparative Antioxidant Potential of Different Moringa Species

Species	Extract Type	Assay	IC_{50} (µg/mL)	Reference
Moringa oleifera	Ethyl acetate	DPPH	40	Verma et al. (2009)
Moringa stenopetala	Aqueous	DPPH	215	Habtemariam and Varghese (2015)
Moringa peregrina	Methanolic	DPPH	17.07	Al-Owaisi et al. (2014)
Moringa concanensis	Methanolic	Hydroxyl Rad.	45.3	Santhi and Sengottuvel (2016)

3.2 Anti – microbial and Anti - viral Potential

Moringa species are extensively utilized as natural water purifiers and antiseptic agents in water treatment due to their potent antimicrobial properties. Seed extracts of M. oleifera and M. stenopetala, particularly those derived using hexane and methanol, have demonstrated significant inhibitory effects against waterborne pathogens such as Salmonella typhi, Vibrio cholerae, and Escherichia coli (Walter et al., 2011). Ethyl acetate, acetone, and ethanol extracts derived from Moringa oleifera seeds, roots, leaves, and their combinations have been evaluated for their antibacterial and antifungal efficacy against oral pathogens (Elgamily et al., 2016). All tested extracts exhibited inhibitory activity against Streptococcus aureus and Streptococcus mutans, with the ethanol and leaf extracts demonstrating the strongest antimicrobial effects. However, none of the extracts showed antifungal activity against Candida albicans. A separate study indicated that significantly higher concentrations of M. oleifera seed extracts were required to suppress the growth of C. albicans (Saadabi and Abu Zaid, 2011). The ethanolic leaf extract of Moringa oleifera was incorporated into both mouthwash and toothpaste formulations (Elgamily et al., 2016). The toothpaste demonstrated inhibitory effects against Streptococcus aureus, S. mutans, and Candida albicans, whereas the mouthwash exhibited only general antimicrobial activity. Ethanolic extracts from the seeds and leaves of Moringa oleifera have also demonstrated antifungal activity against dermatophytic fungi, including Trichophyton mentagrophytes, Microsporum canis, Trichophyton rubrum, and Epidermophyton floccosum (Chuang et al., 2007). Hexane, ethyl acetate, methanol, and chloroform extracts of Moringa oleifera leaves were evaluated for their antibacterial effects against diarrhea-causing pathogens, including Serratia marcescens, Shigella dysenteriae, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, and Salmonella species (Rahman et al., 2010). All extracts demonstrated notable antibacterial activity, with minimum inhibitory concentrations (MICs) ranging from 62.5 to 1,000 µg/mL and inhibition zone diameters varying between 8 and 23.2 mm. The effectiveness of both dried and wet Moringa oleifera leaf powder as a hand-washing agent was evaluated in healthy volunteers. The findings revealed that only the highest concentration tested, 4 g, demonstrated Escherichia coli inhibition comparable to that of a non-medicated liquid soap. The observed antimicrobial activity was found to be independent of mechanical friction during hand washing. Notably, aqueous preparations of M. oleifera leaf powder showed greater antimicrobial efficacy than dried forms, which the study attributed to the presence of saponins compounds with natural surfactant properties (Torondel et al., 2014).

Moringa oleifera extract demonstrated antiviral activity against herpes simplex virus type 1 (HSV-1), inhibiting over 50% of plaque formation at a concentration of 100 µg/mL (Lipipun, V.,Kurokawa, M.,Suttisri, R., Taweechotipatr, P., Pramyothin,P.,Hattori, M., et al. 2003). The extract was effective against phosphonoacetate-resistant and kinase-deficient strains of HSV-1 in mice. At a dosage of 750 mg/kg, it significantly reduced mortality by extending the mean survival time and delaying the onset of skin lesions. Additionally, an aqueous extract of Moringa oleifera leaves enhanced cellular immune responses in HSV-1-infected mice by lowering viral load and suppressing the progression of herpetic skin lesions (Kurokawa et al., 2016). A buffer extract prepared from Moringa oleifera fruits demonstrated notable antiviral activity against the hepatitis B virus (HBV). In addition, a hydroalcoholic extract derived from M. oleifera leaves was shown to significantly reduce the levels of covalently closed circular DNA (cccDNA) of HBV in HepG2 cells a human liver cancer cell line commonly used to study HBV replication. The reduction of cccDNA, which serves as a stable viral reservoir within the nucleus, indicates a potential mechanism by which M. oleifera exerts its anti-HBV effects, making it a promising candidate for further investigation in antiviral therapy development (Waiyaput et al., 2012). A survey reported that Moringa

oleifera is commonly used as a dietary supplement alongside antiretroviral therapy (ART) in the management of HIV infection. Despite its widespread use, there is a lack of rigorous scientific research evaluating the antiviral efficacy of M. oleifera specifically against HIV. Consequently, the therapeutic potential and mechanism of action of this plant in HIV treatment remain largely unexplored, highlighting a significant gap in current antiviral research. Further well-designed studies are needed to determine its effectiveness and safety as an adjunct or alternative antiviral agent (Monera and Maponga, 2010).

3.3 Anticancer and Cytotoxic Properties

Methanol crude extracts of Moringa concanensis root bark inhibited the proliferation of hepatocellular carcinoma (Hep-G2) cells by activating intrinsic apoptotic pathways, specifically through the regulation of caspase-9 and caspase-3, while also causing a reduction in the mitochondrial membrane potential of the cells (Vijayarajan and Pandian, 2016). (4′-O-acetyl-α-L-rhamnopyranosyloxy) benzyl isothiocyanate and niazimicin were identified as key compounds involved in the modulation of caspase-9 activity (Tiloke et al., 2013). Moringa oleifera leaf extract significantly inhibited the proliferation of B16F10 melanoma cells and induced approximately 22% cancer cell death (Gismondi et al., 2013). The extract promoted apoptosis, particularly within the sub-G1 phase of the cell cycle, and caused cell cycle arrest at the G2/M phase. Mechanistically, this effect was associated with the upregulation of key cell cycle regulatory proteins, including p27^Kip1, p53, and p21^WAF1/Cip1, which are known to play critical roles in controlling cell cycle progression and apoptosis. These findings suggest that M. oleifera leaf extract exerts anticancer effects by triggering programmed cell death and halting cell division in melanoma cells. Moringin inhibited malignant astrocytoma cells by inducing apoptosis through oxidative stress, mediated via the activation of Bax and p53 signaling pathways (Rajan et al., 2016). A water extract of Moringa oleifera pods demonstrated significant suppressive effects on mouse colon carcinogenesis induced by dextran sodium sulfate and azoxymethane (Budda et al., 2011). Treatment with the extract led to a marked reduction in the expression of inflammatory markers, including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), alongside a decrease in the proliferating cell nuclear antigen (PCNA) index, indicating lowered cell proliferation in the colon tissue. Furthermore, the extract significantly reduced both the multiplicity and incidence of colon tumors in the mice. The study suggested that the high concentration of omega-9 oleic acid in the extract, known for its anti-inflammatory properties, may play a key role in modulating tumor cell proliferation. Additionally, glucomoringin, a bioactive compound present in M. oleifera, was proposed as a potential contributor to the observed antitumor activity. These findings highlight the multifaceted mechanisms through which M. oleifera pod extracts may exert chemopreventive effects against colon cancer (Budda et al., 2011). A hydroalcoholic extract of Moringa oleifera demonstrated significant antitumorigenic activity by modulating xenobiotic metabolism, effectively balancing the activities of Phase I and Phase II detoxification enzymes (Bharali et al., 2003). Specifically, the extract enhanced the activity of cytochrome P450 (Cyt P450) and cytochrome b5 (Cyt b5) enzymes involved in Phase I metabolism. Concurrently, it increased the levels of key Phase II detoxifying enzymes such as glutathione S-transferase, glutathione reductase, and glutathione peroxidase, while reducing the levels of reduced glutathione (GSH). This suggests that the extract may function as a "blocking agent," reducing the availability of xenobiotic substrates for Phase II metabolism, thereby preventing the formation of harmful metabolites. Additionally, the extract elevated catalase (CAT) concentrations, contributing to enhanced antioxidant defense. These biochemical changes were associated with a reduction in mouse skin papilloma formation and decreased lipid peroxidation, underscoring the extract's potential to protect against chemically induced carcinogenesis by enhancing detoxification and antioxidant mechanisms.

3.4 Anti-diabetic, Anti-lipidemic and Anti-cholesterolemic

Ethanol and aqueous extracts of the aerial parts of Moringa peregrina demonstrated antihyperglycemic effects in streptozotocin-induced diabetic rats by effectively reducing their blood glucose levels (El-Alfy et al., 2011). The hexane fraction obtained from an ethanol extract of the plant lowered blood glucose levels by 64–77.44% within 3 hours, following just 30 minutes of administration. This effect was attributed to the presence of antihyperglycemic compounds, specifically lupeol acetate and β-sitosterol, in the fraction. Additionally, the hydroalcoholic extract of Moringa stenopetala leaves was found to inhibit key enzymes associated with hyperglycemia and hyperlipidemia, including maltase, sucrase, pancreatic cholesterol esterase, pancreatic lipase, and pancreatic α-amylase (Toma et al., 2014). A study demonstrated that an aqueous extract of Moringa oleifera leaves elevated insulin levels and reduced insulin resistance, thereby contributing to the mitigation of hyperglycemia in diabetic rats (Tuorkey, 2016). The extract lowered creatinine and urea levels in impaired kidneys and enhanced immune tolerance in diabetic rats by upregulating the activity of CD69, IFN-γ, and CD44. Additionally, an insulin-like protein was identified in the seed coat of Moringa oleifera (Paula, P. C., Oliveira, J. T., Sousa, D. O., Alves, B. G., Carvalho, A. F., Franco, O. L., et al., 2016). Moringa oleifera has demonstrated a broad spectrum of therapeutic effects in the management of metabolic disorders, particularly diabetes and hyperlipidemia. The extract significantly reduced the expression of interleukin-6 (IL-6), a pro-inflammatory cytokine associated with insulin resistance and systemic inflammation. Additionally, it provided a protective effect on adipocytes by enhancing the expression of heme oxygenase-1 (HO-1), an antioxidant enzyme that plays a crucial role in cellular defense against oxidative stress (Barbagallo et al., 2016). The extract also upregulated the expression of the insulin receptor substrate-1 (IRS-1) gene, a vital component of the insulin signaling cascade, whose deficiency is linked to the development of type 2 diabetes. Furthermore, M. oleifera promoted thermogenesis during adipocyte differentiation by increasing the activity of key thermogenic mediators, including uncoupling protein (UCP), peroxisome proliferator-activated receptor alpha (PPARα), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), all of which are involved in energy metabolism and mitochondrial function. In terms of lipid regulation, the extract at a concentration of 100 µg/mL effectively inhibited HMG-CoA reductase, a key enzyme in cholesterol biosynthesis, showing comparable efficacy to 0.4 µg/mL of pravastatin (Duangjai et al., 2011). Moreover, M. oleifera exhibited synergistic effects when combined with sitagliptin, enhancing antihyperglycemic activity and delaying the progression of lenticular opacity in diabetic rats (Olurishe et al., 2016). These findings underscore the potential of M. oleifera as a multifunctional botanical intervention in the treatment and prevention of diabetes and its related complications. A differential response in high-density lipoprotein (HDL) levels was observed when Moringa oleifera was administered to normal versus hypercholesterolemic rabbits. In normal rabbits, M. oleifera supplementation led to a reduction in HDL levels. Conversely, in hypercholesterolemic rabbits, the same treatment resulted in a significant elevation of HDL levels, suggesting a context-dependent modulation of lipid metabolism (Mehta et al., 2003; Nunthanawanich et al., 2016).

This biphasic effect implies that M. oleifera may help restore lipid homeostasis under pathological conditions, while slightly altering lipid balance in normolipidemic states. In addition to influencing HDL levels, M. oleifera demonstrated a lipid-lowering effect across multiple organs. The total lipid content in the aorta, heart, and liver of hypercholesterolemic rabbits was markedly reduced following treatment. This reduction in tissue lipid accumulation indicates that M. oleifera not only modulates systemic lipid parameters but also provides organ-specific protection against lipid infiltration and potential atherosclerotic damage. These findings highlight its therapeutic potential in the management of cardiovascular diseases associated with dyslipidemia.

Table 3: Anti-diabetic, Anti-lipidemic, and Anti-cholesterolemic Activities of Moringa Species

Moringa Species	Extract Type / Fraction	Experimental Model	Observed Effect / Mechanism	Reference
M. peregrina	Ethanol and aqueous aerial extracts	STZ-induced diabetic rats	↓ Blood glucose; lupeol acetate and β-sitosterol contribute to antihyperglycemic activity	El-Alfy et al., 2011
M. oleifera	Hydroalcoholic leaf extract	Diabetic rats	↑ Insulin, ↓ Insulin resistance, ↓ Creatinine & urea; immune tolerance improvement via CD69, IFN-γ, CD44	Tuorkey, 2016

Table 3 (cont) : Anti-diabetic, Anti-lipidemic, and Anti-cholesterolemic Activities of Moringa Species				
M. stenopetala	Hydroalcoholic leaf extract	Enzyme inhibition assays	Inhibited α-amylase, sucrase, maltase, lipase, and cholesterol esterase	Toma et al., 2014
M. oleifera	Seed coat protein isolate	In vitro / diabetic rats	Presence of insulin-like protein improves glucose utilization	Paula et al., 2016
M. oleifera	Leaf extract	Adipocytes & cell lines	↑ HO-1, ↓ IL-6, ↑ IRS-1 expression; protects adipocytes and improves insulin signalling	Barbagallo et al., 2016
M. oleifera	Ethanolic leaf extract	Enzyme inhibition in vitro	Inhibits HMG-CoA reductase; comparable to pravastatin in lipid biosynthesis inhibition	Duangjai et al., 2011
M. oleifera	Leaf extract + sitagliptin	Diabetic rats	Synergistic antihyperglycemic effect; delayed lenticular opacity	Olurishe et al., 2016
M. oleifera	Fruit supplementation	Normal & hypercholesterolemic rabbits	↓ HDL in normals, ↑ HDL in hypercholesterolemic; restores lipid homeostasis	Mehta et al., 2003
M. oleifera	Leaf extract	Hyperlipidemic rabbit model	↓ Lipid levels in aorta, heart, and liver; protects against atherosclerosis	Nunthanawanich et al., 2016
M. peregrina	Hexane fraction from ethanol extract	Diabetic rats	↓ Blood glucose (64–77.44%) within 3 hours; rapid onset effect attributed to lipophilic bioactives	El-Alfy et al., 2011

4. Future Directions and Perspectives

4.1 Underexplored Moringa Species: A Bioprospective Opportunity

Moringa hildebrandtii represents a remarkable yet underexplored species with considerable bioprospective potential. Native to Madagascar, this species is a member of the family Moringaceae and shares the economic and pharmacological promise attributed to its better-known relatives, such as Moringa oleifera. However, unlike its widely studied counterpart, M. hildebrandtii remains significantly under-investigated despite being preserved through traditional horticultural practices even after its extinction in the wild.

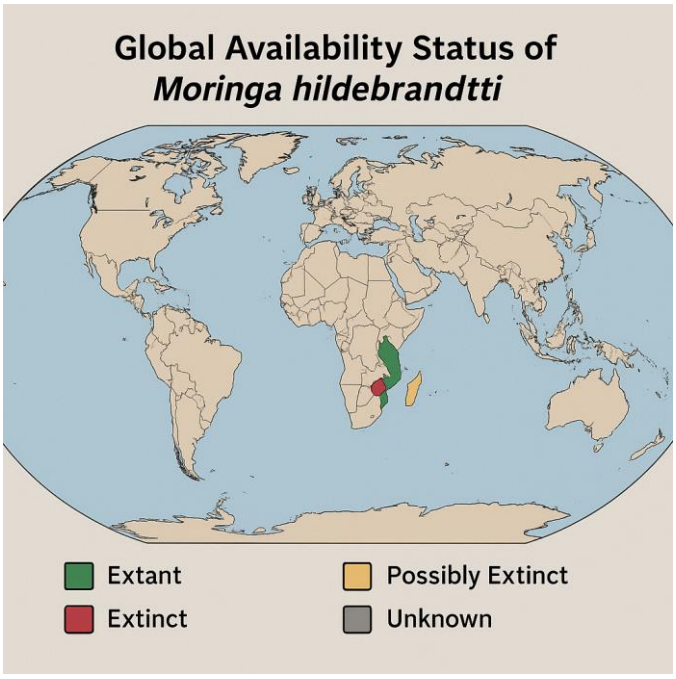


Figure 2: Global Availability Status of Moringa hildebrandtii.

4.1.1 Ecological and Botanical Significance

M. hildebrandtii is a large, bottle-shaped tree characterized by its water-storing trunk and tripinnate leaves. It is known for its fast growth and ornamental value. Although extinct in the wild, it is still abundantly cultivated in southern and western Madagascar, particularly in villages, where it is used in ceremonies, planted around graves, and sometimes utilized for medicinal purposes.

4.1.2 Extinction in the Wild and Cultural Conservation

The species has not been observed in the wild despite extensive fieldwork and interviews with local inhabitants. All known specimens have been collected from cultivated areas, suggesting a unique case of cultural preservation of a species long extinct in its natural habitat. The vernacular name "hazomaroseranana" implies historical linkage with the Maroseranana region and people, further hinting at its original geographical range in the arid southwest of Madagascar.

4.1.3 Prospective Biotechnological and Pharmacological Applications

Given the established bioactivity of other Moringa species (e.g., hypocholesterolemic effects, water purification agents, and antimicrobial properties in M. oleifera), M. hildebrandtii likely harbors valuable phytochemicals that warrant further study. Previous ethnobotanical reports note the use of its pulpy wood for medicinal purposes, although systematic pharmacological profiling is lacking.

4.1.4 Research Opportunities

- Comparative phytochemistry: Comparing M. hildebrandtii with M. oleifera and M. drouhardii can help identify unique secondary metabolites or bioactivities.
- Ethnobotany and conservation biology: Investigating traditional uses and the role of cultural practices in species preservation may offer models for conservation of other threatened species.
- Genetic and ecological studies: As it shows close relation to M. drouhardii, genetic analyses could provide insights into its evolutionary history and resilience traits.

4.1.5 Conservation Implications

Despite being functionally extinct in the wild, the survival of M. hildebrandtii in cultivation provides a rare opportunity for ex-situ conservation. However, reintroduction is currently unfeasible due to the unknown native habitat and potential loss of ecological interactions. Nonetheless, the tree's continued cultivation by local communities offers a living genetic repository with untapped potential for ecological restoration or bioprospecting (Olson and Razafimandimbison, 2000; Ghasi et al., 2000; Oliveira et al., 1999).

5. Conclusion

The genus Moringa holds extraordinary promise as a reservoir of specialized metabolites with diverse pharmacological activities, ranging from antioxidant and anti-inflammatory effects to anticancer, antidiabetic, and antimicrobial potentials. While Moringa oleifera has emerged as a globally recognized phytopharmaceutical and nutraceutical agent, the majority of species within the genus particularly those endemic to Madagascar and Northeast Africa remain critically underexplored. Among these, Moringa hildebrandtii represents a unique bioprospective opportunity. Despite its extinction in the wild, this species continues to thrive under traditional horticultural practices in Madagascar, serving as a living testament to indigenous conservation and ethnobotanical

heritage. Its unique morphology, potential for water storage, and ceremonial and medicinal use suggest a wealth of unexplored bioactive compounds, yet it has received minimal phytochemical or pharmacological investigation. This review underscores the urgent need to expand research beyond the well-studied M. oleifera, applying integrative methodologies such as omics-based profiling, bioassay-guided fractionation, and comparative genomics to unveil the hidden phytochemical landscapes of lesser-known species like M. hildebrandtii, M. drouhardii, and M. ovalifolia. Moreover, ethnobotanical insights and cultural practices surrounding these species may offer novel conservation models and contextual frameworks for sustainable utilization. In summary, the untapped biodiversity within the Moringa genus represents both a scientific frontier and a conservation imperative. Harnessing this potential will not only expand our pharmacognostic and biotechnological repertoire but also reinforce the importance of preserving traditional ecological knowledge and endemic plant diversity.

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