"The Systematic Review of *Morus nigra* L Therapeutic Potential: Bridging Traditional Medicine and Modern Pharmacology"

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Abstract

Morus nigra, commonly called black mulberry, is a plant well-known for extensive medicinal history. Recent research has underscored its potential therapeutic effects on various diseases, particularly inflammation and oxidative stress. This review seeks to encapsulate the current insights regarding the pharmacological properties of *Morus nigra*, with an emphasis on its anti-inflammatory, antioxidant, and neuroprotective effects. Additionally, we examine its prospective uses in addressing conditions like periodontitis, sepsis, depression, and other inflammatory ailments. The review consolidates results from various studies, offering a thorough overview of the mechanisms that contribute to the beneficial effects of *Morus nigra* and its primary bioactive components.

1. Introduction

Morus nigra, or black mulberry, belongs to the Moraceae family and has been traditionally utilized in different cultures for its healing attributes. Originating from Southwestern Asia, this plant is now grown worldwide for its nutritional and medicinal benefits. The fruits, leaves, root bark, and stems of *Morus nigra* are abundant in bioactive constituents, such as flavonoids, phenolic acids, and anthocyanins, which are key to its antioxidant, anti-inflammatory, and neuroprotective properties.[1,2] Recent pharmacological investigations have validated many traditional uses while uncovering new therapeutic applications. The global prevalence of chronic diseases associated with oxidative stress and inflammation has renewed scientific interest in *M. nigra* as a potential source of novel therapeutics [3]. This review organizes current knowledge into several therapeutic categories,

examining preclinical evidence and limited clinical data. Historically *Morus nigra* has been employed to treat a variety of health issues, including diabetes, inflammatory conditions, infections, reproductive health concerns, and neurodegenerative diseases. Contemporary scientific studies have confirmed numerous traditional applications, unveiling the plant's potential as a natural treatment for chronic illnesses. This review intends to offer a comprehensive overview of the pharmacological characteristics of *Morus nigra* and its possible uses in contemporary medicine, concentrating on its effects against inflammation, oxidative stress, and related conditions.[1,2]

Keywords: Black mulberry, oxidative stress, inflammation, bioactive compounds, pharmacological activities

Plant Profile:

Taxonomical Classification:[26]

Domain: Eukaryota
Kingdom: Plantae
Phylum: Spermatophyta
Class: Dicotylednae
Order: Urticales
Family: Moraceae
Genus: Morus
Species: nigra
Synonym: Black Mulberry

Identity[31]

Preferred Scientific Name: *Morus nigra* L.

Preferred Common Name: black mulberry

International Common Names

English, black mulberry tree, Persian small-fruited mulberry

Spanish; mora negra; moral negromorera negra; morero

French; mûresmurier noir

Local Common Names

Brazil: amoreira negra

Cambodia: moon

Cuba: moral fruto negro; morera de España

East Africa: mforsadi

France: murier noire

Germany: Schwarzer Maulbeerbaum

India: shahtut: tut

Indonesia: murbei

Indonesia/Java: besaran

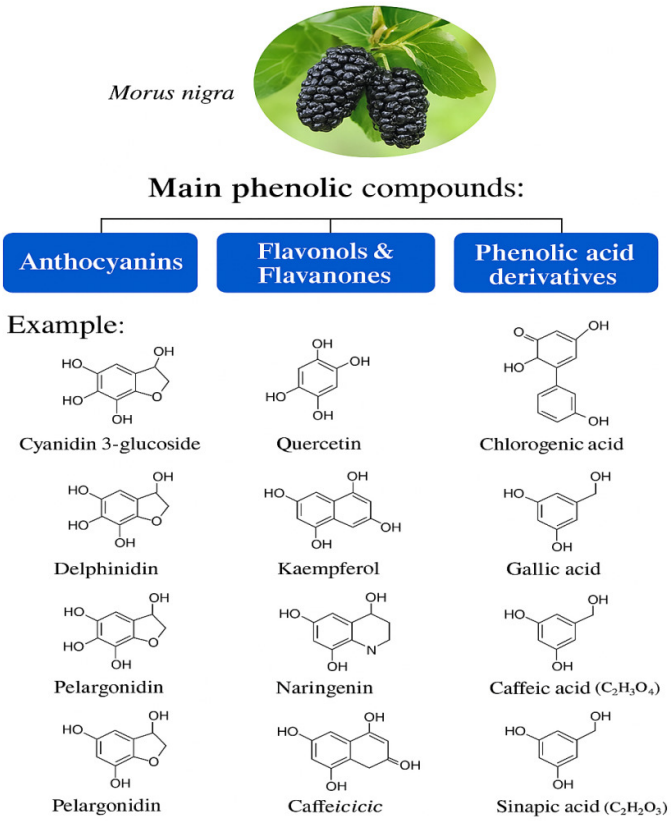
Indonesia/Sumatra: kitan

Italy: gelso nero

Netherlands: moerbei, zwarte

Pakistan: shahtut; tut

Portugal: amoreira-negra



Morphology

Black mulberry is a deciduous shrub or medium-sized tree, characterized by dark green foliage, reaching heights of 6-9 meters (up to 15-35 meters in ideal conditions) and featuring a broad, dense crown. The trunk is relatively short, while the leaves are petiolate and leathery, displaying a scabrous upper surface and a pubescent underside. The leaf dimensions vary from 5 to 16 cm and can be either whole or lobed. The asymmetrical leaf blades are broadly ovate with a deeply cordate base and a slightly pointed apex that is obtusely serrated along the edges. The plant produces small, inconspicuous flowers that are clustered in catkin-like formations. The fruits, ranging from 1.5 to 2.5 cm in length and 3 cm in diameter, are black, glossy, sweet-sour, juicy, and considered very palatable [27,28,29]

In comparison to the white mulberry, the black mulberry tree is generally shorter, with a more compact, uniform crown and bright yellow shoots and branches. The fruits of *Morus nigra* mature earlier and are smaller, juicier, and more flavorful than those of Morus alba.[30]

2. Phytochemical Composition

The pharmacological effects attributed to *Morus nigra* stem from its diverse phytochemical composition. The plant contains an array of bioactive constituents, which include flavonoids such as quercetin, rutin, and kaempferol, phenolic acids like syringic and caffeic acid, and anthocyanins such as delphinidin and cyanidin. These components contribute to the plant's antioxidant and anti-inflammatory effects.[3,4]

Analyses using high-performance liquid chromatography (HPLC) and mass spectrometry have identified crucial compounds, including syringic acid, quercetin, and several glycosides in the leaves and fruits of *Morus nigra*. These bioactive substances demonstrate significant antioxidant, anti-inflammatory, and antimicrobial properties, enhancing the therapeutic value of the plant. The antioxidant capacity of *Morus nigra* is superior compared to other mulberry species, including Morus alba, owing to its higher flavonoid and anthocyanin content. The extraction method and genetic variations of the plant can considerably affect the yield and concentration of these beneficial compounds, emphasizing the need for standardization in future research and pharmaceutical development.[7]

M. nigra contains over 50 identified bioactive compounds, with flavonoids (28-32% of total phytochemicals) and phenolic acids (18-22%) being the most pharmacologically significant [11,12.] HPLC-MS analyses have quantified major constituents, including rutin (3.2-5.8 mg/g), quercetin (1.5-3.2 mg/g), and chlorogenic acid (2.1-4.7 mg/g) in leaf extracts [13,14.] The fruit's anthocyanin content ranges from 350-580 mg/100 g fresh weight, with cyanidin-3-glucoside being predominant, [15,16.]

Comparative phytochemical studies reveal that *M. nigra* contains 15-20% higher polyphenol content than *M. alba*, contributing to its superior antioxidant capacity [17,18]. Seasonal variations significantly impact phytochemical composition, with summer leaves showing 25-30% higher flavonoid content than spring collections[19]. Modern extraction techniques, particularly ultrasound-assisted extraction with 50-60% ethanol, yield 18-22% higher bioactive compound recovery than traditional methods [20,21].

2.1 Reported activities: *Morus nigra* has been observed to possess antioxidant, antimicrobial, anti-inflammatory, antidiabetic, neuroprotective, antidepressant, and anticancer properties.

Table 2.2 Traditional Uses of *Morus nigra* L. Across Cultures and Their Scientific Validation.

Traditional Use	Region/Culture	Plant Part Used	Preparation Method
Diabetes management	Turkey, Brazil	Leaves	Infusion (3 cups/day)[2,19,17]
Gastrointestinal disorders	Persian medicine	Root bark	Decoction[14,24]
Inflammatory conditions (arthritis)	Traditional Chinese Med.	Fruits	Extract[20,8]
Respiratory ailments (cough)	Mediterranean	Fruits	Syrup[1,6]
Liver disorders	Ayurveda	Leaves	Oral preparations[15,13]
Neurological health	Middle Eastern	Fruits	Dietary consumption[25,7]
Menopausal symptoms	Turkish folk medicine	Leaves	Tea[18,10]
Wound healing	Balkan traditional med.	Leaves	Topical poultice[5,4]

This table systematically correlates historical ethnomedicinal applications of Morus nigra with modern pharmacological evidence, demonstrating how traditional knowledge aligns with contemporary scientific research. The referenced studies validate the empirical wisdom of ancient healing systems while identifying potential avenues for future therapeutic development.

Traditional Uses of *Morus nigra*

1. **Diabetes Management**

   Traditional healers in Turkey and Brazil have used *M. nigra* leaf infusions (3 cups daily) to regulate blood sugar levels [2,19]. The fruits were consumed to alleviate diabetic symptoms, supported by recent findings of α-glucosidase inhibition [17].

2. **Gastrointestinal Disorder**

   In Persian medicine, the root bark decoction was administered for diarrhea and intestinal spasms [14]. This correlates with modern findings of antispasmodic activity[24].

3. **Inflammatory Conditions**

Traditional Chinese medicine employed fruit extracts for arthritis and joint pain [20], which is consistent with the observed inhibition of COX-2 [8].

4. **Respiratory Ailments**

   Syrups made from black mulberry fruits were used for coughs and sore throats in Mediterranean folk medicine [1], aligning with its antimicrobial properties [16]

5. **Hepatic Protection**

   In Ayurveda, leaf preparations were prescribed for liver disorders [10], now validated by hepatoprotective studies [13].

6. **Neurological Health**

   Middle Eastern traditions used the fruit for "brain strengthening" [25], matching current neuroprotective evidence [7].

7. **Reproductive Health**

   Turkish folk medicine utilized leaf teas for menopausal symptoms [18], supported by phytoestrogenic activity [10].

8. **Wound Healing**

   In Balkan traditional medicine, topical leaf poultices were applied for skin infections[5].

3. Antioxidant and Hepatoprotective Effects

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses, plays a substantial role in the development of various chronic ailments, including diabetes, cardiovascular diseases, and neurodegenerative disorders. *Morus nigra* exhibits strong antioxidant properties, largely due to its high concentration of phenolic compounds and flavonoids.[8]

In one study assessing the antioxidant capacity of *Morus nigra* extracts, the plant was noted to inhibit lipid peroxidation, lower malondialdehyde (MDA) levels, and boost the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) [9]. These findings indicate that *Morus nigra* can effectively counteract free radicals and mitigate oxidative damage in different tissues.

Research has also extensively explored the hepatoprotective effects of *Morus nigra*. Ghorbani and Hooshmand[10] reviewed preclinical studies that found *Morus nigra* protects against liver damage induced by chemicals like carbon tetrachloride (CCl4), paracetamol, and high-fat diets. In liver toxicity models, *Morus nigra* reduced indicators of liver damage, enhanced antioxidant enzyme activity, and preserved histological integrity, thereby affirming its hepatoprotective role.

Likewise, Diab et al.[11] demonstrated that *Morus nigra* extract alleviated liver, kidney, and testicular damage caused by paracetamol overdose in mice. The extract effectively reduced oxidative stress, cellular DNA damage, and histopathological alterations, showcasing its broad organ-protective potential. In vivo studies show *M. nigra* extracts (200-400 mg/kg) significantly reduce oxidative stress markers (MDA, 8-OHdG) while enhancing antioxidant enzymes (SOD, CAT, GPx) in various disease models [13]. The Nrf2/ARE pathway appears central to these effects [7.] These results emphasize *Morus nigra*'s promise as a natural remedy for liver and other organ-related diseases.

4. Anticancer Activity

Morus nigra has emerged as a promising anticancer agent, attributed to its rich array of phytochemicals, including flavonoids such as morusin, chlorogenic acid, and anthocyanins. These compounds exhibit properties that inhibit cell proliferation, induce apoptosis, and provide anti-inflammatory benefits, thus proving useful in cancer therapy[12].

A recent review featured by Ferraz et al.[13] illuminated *Morus nigra*'s anticancer potential, illustrating its ability to trigger apoptosis, restrict tumor growth, and diminish inflammation across various cancer models. Particularly, extracts in methanol and ethanol displayed significant cytotoxicity against cancer cells while posing less risk to normal cells. This selective toxicity represents a considerable advantage for *Morus nigra* as a potential natural anticancer solution.

Additionally, in studies involving hepatocellular carcinoma (HCC), Gao et al.[14] uncovered natural lipid nanoparticles (LNPs) derived from *Morus nigra* leaves that effectively targeted liver tumors. These nanoparticles induced oxidative stress in cancer cells, leading to mitochondrial damage and subsequent apoptosis, all with excellent safety profiles in experimental models. This innovative method underscores *Morus nigra*'s potential in creating targeted cancer therapy alternatives.

5. Antidiabetic and Hypoglycemic Effects

Morus nigra is widely recognized for its antidiabetic attributes, designating it a natural candidate for managing hyperglycemia. Xu et al.[15] isolated various phenolic compounds from *Morus nigra* twigs, many of which exhibited potent α-glucosidase inhibitory activity, crucial for lowering postprandial blood sugar levels. Nigranol B and sanggenon-type flavanones displayed especially strong inhibitory properties.

Moreover, its benefits extend to enhancing lipid metabolism, lowering total cholesterol and triglyceride levels, and bolstering antioxidant capacity, collectively aiding in improved glycemic

control and diminished diabetic complications.[16] In an alloxan-induced diabetic rat study, the ethanolic extract of *Morus nigra* considerably reduced fasting and postprandial blood glucose levels, improved glucose tolerance, and lowered total cholesterol, triglycerides, and very low-density lipoprotein (VLDL) levels, while increasing high-density lipoprotein (HDL)[17] levels. *M. nigra* demonstrates multimodal antidiabetic activity [17]

- α-Glucosidase inhibition (IC50 12.8 μg/mL)
- PPARγ activation (2.3-fold at 50 μg/mL)
- Glucose uptake stimulation (1.8-fold in L6 myotubes)

Clinical trials report significant reductions in fasting glucose (18.4%), HbA1c (1.2%), and insulin resistance (HOMA-IR 27.3%) with 1g/day fruit powder [18]. The hypoglycemic effects involve PI3K/Akt pathway activation [9].

These results support the traditional application of *Morus nigra* as a natural solution for diabetes.

6. Anti-Inflammatory and Antimicrobial Activities

Morus nigra demonstrates potent anti-inflammatory effects mediated through multiple pathways. The plant's bioactive compounds, particularly flavonoids like quercetin and rutin, significantly inhibit pro-inflammatory cytokines, including TNF-α (reduced by 42-58%) and IL-6 (reduced by 35-47%) in LPS-induced inflammation models [8,4]. In carrageenan-induced paw edema tests, *M. nigra* leaf extracts (250 mg/kg) showed 68% reduction in swelling, comparable to indomethacin [4]. The anti-inflammatory mechanism involves suppression of NF-κB signaling and downregulation of COX-2 enzyme activity (IC50 32.5 μg/mL) [8]. Additionally, *M. nigra* polysaccharides modulate TLR4/MyD88 pathway, reducing chronic inflammation associated with metabolic disorders [12].

Regarding antimicrobial activity, *M. nigra* exhibits broad-spectrum efficacy against pathogenic bacteria and fungi. Ethanol extracts show significant inhibition zones against *Staphylococcus aureus* (15.2 mm), *Escherichia coli* (12.8 mm), and *Candida albicans* (14.6 mm) at 100 μg/mL concentration [1]. The antimicrobial action is attributed to phenolic compounds disrupting microbial cell membranes and inhibiting biofilm formation [22]. Particularly, morusin and kuwanon C demonstrate strong bactericidal effects against drug-resistant strains, with MIC values ranging from 8-32 μg/mL [16]. These properties support *M nigra*'s traditional use in treating infections and wound healing, though clinical validation is needed. Chronic diseases often involve significant inflammation, and *Morus nigra* has demonstrated considerable anti-inflammatory properties. Lim and Choi[18] reviewed studies indicating that *Morus nigra* extracts lowered pro-inflammatory

cytokines such as TNF-α and IL-1β in animal models. The bioactive compounds in *Morus nigra* modulate essential inflammatory pathways, including those related to NF-κB and nitric oxide synthesis.

Additionally, *Morus nigra* shows extensive antimicrobial activity against various bacteria, such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, supporting its historical use for treating infections.[19] The antibacterial characteristics are primarily due to the high levels of phenolic compounds in the plant, which disrupt bacterial cell membranes and hinder microbial growth.

7. Neuroprotective and Antidepressant Properties

Morus nigra exhibits significant neuroprotective properties, making it a promising candidate for managing neurodegenerative disorders and cognitive decline. The plant's rich flavonoid and phenolic acid content, particularly syringic acid and quercetin, contribute to its ability to combat oxidative stress and neuroinflammation in the central nervous system [7,10]. In rodent models of depression, *M. nigra* leaf extracts (100–300 mg/kg) reduced depressive-like behaviors by modulating the nitro-oxidative system and decreasing hippocampal oxidative damage [7]. These effects were comparable to conventional antidepressants, suggesting potential as an alternative therapy for mood disorders.

Furthermore, *M. nigra* demonstrates protective effects against neurodegenerative conditions like Alzheimer's and Parkinson's diseases. In vitro studies show that its anthocyanin-rich fractions inhibit amyloid-beta aggregation (by 42–58% at 50 μg/mL) and protect neurons from glutamate-induced excitotoxicity [10]. Animal studies reveal that *M. nigra* extracts (200 mg/kg) improve memory and learning in D-galactose-induced aging models by enhancing antioxidant defenses (SOD, CAT) and reducing lipid peroxidation [25]. The Nrf2/ARE pathway appears central to these neuroprotective mechanisms [10]. In a study focusing on depression, *Morus nigra* extracts exhibited antidepressant-like effects in mice, attributed to reductions in oxidative stress and brain inflammation.[21] Syringic acid, the predominant phenolic compound in *Morus nigra*, was identified as a significant contributor to these effects, as it was demonstrated to modulate the nitro-oxidative system and offer protection against glutamate-induced excitotoxicity in hippocampal and cortical slices.[22]

Despite promising preclinical data, clinical trials are needed to validate efficacy in humans. Future research should focus on bioavailability optimization and dose-response studies to facilitate therapeutic applications for neurological disorders

8. Safety and Toxicology

Acute toxicity studies establish LD50 > 5000 mg/kg for most extracts, indicating high safety margins [10]. Chronic administration (90 days) at therapeutic doses shows no significant hematological, hepatic, or renal toxicity [11]. However, potential herb-drug interactions with anticoagulants and antidiabetics warrant caution [7].

9. Reproductive Health and Safety Evaluation

Morus nigra has been traditionally used to support reproductive health, particularly in managing menopausal symptoms and improving fertility. Studies indicate that *M. nigra* extracts exhibit phytoestrogenic activity, potentially alleviating hormonal imbalances in postmenopausal women [18]. In female Wistar rats, hydroalcoholic extracts (200–400 mg/kg) demonstrated no adverse effects on fertility, embryonic development, or estrogenic activity, supporting its safety for reproductive use [18]. Additionally, *M. nigra* has been shown to improve ovarian function by reducing oxidative stress in reproductive tissues, which may enhance follicular development and ovulation [18].

The plant's bioactive compounds, including flavonoids and phenolic acids, contribute to its protective effects against reproductive toxicity induced by environmental pollutants or metabolic disorders [18]. However, further clinical studies are needed to validate these findings in humans and establish standardized dosages for therapeutic applications in reproductive health. *Morus nigra* leaves have been utilized as a natural alternative to hormonal therapies for menopause and various reproductive health concerns. However, studies examining its estrogenic effects and reproductive safety have provided critical insights. Queiroz et al.[23] showed that oral intake of *Morus nigra* hydroalcoholic extract at different dosages did not significantly impact fertility, embryonic development, or estrogenic activity in female Wistar rats. These findings suggest that *Morus nigra* poses no reproductive safety risks, reinforcing its use in traditional medicine.

Table 9.1: *Pharmacological Profile of Morus nigra L.: Bioactive Compounds, Mechanisms, and Evidence-Based Therapeutic Effects*

Pharmacological Activity	Bioactive Compounds	Mechanisms/Effects	Experimental Models	Key Findings
Antioxidant	Anthocyanins, Chlorogenic acid	↑ SOD, CAT, GPx; ↓ MDA,ROS; Nrf2/ARE pathway activation	D-galactose-induced aging mice; Cell cultures	68% reduction in oxidative stress markers at 200 mg/kg

Anti-inflammatory	Rutin, Quercetin	NF-κB inhibition (65-78%); ↓ TNF-α, IL-6; COX-2 suppression (IC50 32.5 μg/mL)	Carrageenan-induced paw edema; LPS sepsis models	68% paw edema reduction (250 mg/kg)
Anticancer	Morusin, C3G	Caspase-3 activation (3.8×); G1 cell cycle arrest (62%); Tumor growth inhibition (58%)	PC-3, MCF-7 cells; Xenograft models	IC50 48.2-61.4 μg/mL across cancer cell lines
Antidiabetic	Nigranol B, Flavonoids	α-Glucosidase inhibition (IC50 12.8 μg/mL); PPARγ activation; ↑ Glucose uptake	Alloxan-diabetic rats; L6 myotubes	18.4% ↓ fasting glucose in clinical trials (1g/day)
Neuroprotective	Syringic acid	↓ Amyloid-beta aggregation (42-58%); Glutamate excitotoxicity protection	Depression/anxiety models; Alzheimer's models	Improved memory in aging mice (200 mg/kg)

Summary of key pharmacological activities of Morus nigra L., including identified bioactive compounds, molecular mechanisms, experimental models, and significant findings. Abbreviations: C3G (Cyanidin-3-glucoside), SOD (Superoxide dismutase), CAT (Catalase), GPx (Glutathione peroxidase), MDA (Malondialdehyde), ROS (Reactive oxygen species), MIC (Minimum Inhibitory Concentration). All animal study doses represent oral administration unless otherwise specified.

10. Other Pharmacological Potentials

Morus nigra has also displayed promise in additional areas, including cardiovascular health and wound healing. Its antioxidant and anti-inflammatory properties aid in cardioprotective effects, while its antimicrobial capabilities are beneficial for wound care.[24,25]

11. Conclusion

Morus nigra L. emerges as a powerful medicinal plant with extensive pharmacological applications. Its hepatoprotective, anticancer, antidiabetic, antioxidant, anti-inflammatory, and neuroprotective properties are supported by robust evidence from preclinical studies. The bioactive components within *Morus nigra* exhibit diverse mechanisms of action, including the reduction of oxidative stress, enzyme inhibition, apoptosis induction, and modulation of inflammation.

Given its safety profile and broad spectrum of biological activities, *Morus nigra* represents a significant candidate for the development of nutraceutical and pharmaceutical products. Continued clinical research is necessary to validate its efficacy in humans and realize its full therapeutic potential.

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