**Review Article**

**Health-Promoting Polyphenols in Mulberry Fruits: A Comprehensive Review**

**Abstract**

Mulberry (*Morus* spp.) fruits are a rich source of polyphenolic compounds, including anthocyanins, flavonoids and phenolic acids, which contribute to a broad spectrum of biological activities. These naturally occurring phytochemicals exhibit potent antioxidant, anti-inflammatory, antidiabetic, cardioprotective, neuroprotective and anti-obesity effects. Their mechanisms of action involve the modulation of oxidative stress, inhibition of pro-inflammatory pathways, regulation of glucose and lipid metabolism and enhancement of cellular defense systems. Recent advances in phytochemical analysis and biomedical research have highlighted the potential of mulberry polyphenols as functional food components and therapeutic agents. This review comprehensively explores the composition, pharmacological effects and molecular mechanisms of polyphenols present in mulberry fruits, while also addressing current challenges in bioavailability and formulation. The findings support the integration of mulberry-based polyphenols into preventive health strategies and suggest promising avenues for future nutraceutical development.

*Keywords: Mulberry fruit; Polyphenols; Anthocyanins; Flavonoids; Antioxidants; Human health; Morus spp.*

**1. Introduction**

Polyphenols are a diverse class of naturally occurring secondary metabolites found abundantly in plant-based foods, particularly fruits and vegetables. They are well-known for their potent biological activities, including antioxidant, anti-inflammatory, antidiabetic and cardioprotective properties (Pandey & Rizvi, 2009). Among the various polyphenol-rich fruits, mulberries (*Morus* spp.) have gained significant scientific attention due to their high content of phenolic compounds such as anthocyanins, flavonoids and phenolic acids (Ercisli & Orhan, 2007).

Mulberry fruits have been traditionally used in Asian medicine to treat fever, sore throat and diabetes and are now recognized globally for their potential as functional foods (Butt *et al*., 2008). The polyphenolic profile of mulberries varies by species, cultivar, and maturity stage, with Morus nigra and Morus alba being the most widely studied for their bioactive potential (Li *et al*., 2012). These polyphenols exert multiple beneficial effects on human health by scavenging free radicals, modulating oxidative stress pathways, reducing pro-inflammatory cytokines, and regulating glucose and lipid metabolism (Ozcan *et al*., 2014; Chen *et al*., 2016).

The increasing global burden of non-communicable diseases such as diabetes, obesity, cardiovascular diseases, and neurodegenerative disorders has intensified research on natural plant-based therapies. In this context, mulberry-derived polyphenols have emerged as promising bioactive candidates. Numerous *in vitro* and *in vivo* studies have demonstrated their efficacy in ameliorating hyperglycemia, lowering blood pressure, reducing oxidative DNA damage, and enhancing neuroprotection (Hu *et al*., 2025).

Despite the growing interest, a focused and comprehensive evaluation of the specific classes of polyphenols in mulberry fruits, their distribution, mechanisms of action, and therapeutic implications remains limited. This review aims to consolidate current knowledge on the polyphenolic composition of mulberry fruits, evaluate their functional and pharmacological properties, and discuss their potential roles in human health and disease prevention.

**2. Polyphenol Composition in Mulberry Fruits**

**2.1 Total Phenolic Content**

Polyphenols in mulberry fruits are primarily composed of anthocyanins, flavonoids and phenolic acids, all of which are responsible for the plant’s antioxidant capacity and health-promoting properties. The total phenolic content (TPC) of mulberry varies significantly depending on the species, fruit maturity, cultivation conditions and extraction methods. Studies report that *Morus nigra* typically exhibits higher TPC compared to *Morus alba* and *Morus rubra* due to its deep pigmentation and higher anthocyanin concentration (Ercisli & Orhan, 2007). The polyphenol composition of mulberry fruit is presented in Table 1.

For instance, Wang *et al.* (2022) measured TPC values ranged from 10.82 mg to 27.29 mg  gallic acid equivalents (GAE)/ g dry weight in different mulberry genotypes. Polyphenol content also tends to increase with fruit ripening, a trend attributed to the accumulation of anthocyanins and the enzymatic conversion of precursor compounds (Kapoor *et al.,* 2022). Furthermore, environmental factors like altitude and soil composition may modulate phenolic biosynthesis, which may explain regional variations in antioxidant potency (Sánchez-Salcedo *et al*., 2015).

**Table 1: Overview of Polyphenol Content in Mulberry Fruit**

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| **Class** | **Subclass** | **Compound** | **Content** | **References** |
| Flavonoids | Anthocyanins | Cyanidin-3-glucoside | 301.75 mg/g MAEa | Chen *et al.,* 2016, Chang *et al*., 2013 |
|  |  | Cyanidin-3-rutinoside | 108.79 mg/g MAE | Chen *et al.,* 2016, Chang *et al*., 2013 |
|  |  | Pelargonidin-3-glucoside | NA | Huang *et al.,* 2008, Liu *et al.,* 2009 |
|  |  | Pelargonidin-3-rutinoside | NA | Huang *et al.,* 2008, Liu *et al.,* 2009 |
|  |  | Cyanidin 3-O-(6″-O-α-rhamnopyranosyl-β-D-glucopyranoside) | 270 mg/g CMA | Du *et al.*, 2008 |
|  |  | Cyanidin 3-O-(6″-O-a-rhamnopyranosyl-β-D-galactopyranoside) | 57 mg/g CMA | Du *et al.*, 2008 |
|  |  | Cyanidin 3-O-β-D-galactopyranoside | 233 mg/g CMA | Du *et al.*, 2008 |
|  |  | Cyanidin 7-O-β-D-glucopyranoside | 33 mg/g CMA | Du *et al.*, 2008 |
|  |  | Petunidin 3-O-β-glucopyranoside | 5.1 mg/g CEE | Sheng *et al.,* 2014 |
|  | Flavonols | Rutin | 0.065−7.728 mg/100 g FW | Natic *et al*., 2015 |
|  |  | Quercetin | 31.88−58.42 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Quercetin 3-O-rutinoside | 2.869 mg/100 g FW | Jin *et al.,* 2015 |
|  |  | Quercetin 3-O-glucoside | 1.069 mg/100 g FW | Jin *et al.,* 2015 |
|  |  | Quercetin 3-O-galactoside | 0.002 mg/100 g FW | Jin *et al.,* 2015 |
|  |  | Myricetin | 0.66−1.18 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Kaempferol | 0.24−1.61 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Kaempferol 3-O-glucoside | 1.623 mg/100 g FW | Jin *et al.,* 2015 |
|  |  | Kaempferol 3-O-rutinoside | 2.00−14.00 mg/100 g DW | Sánchez-Salcedo *et al*., 2015 |
|  | Flavanols | Catechin | 309.26−750.01 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Epigallocatechin Gallate | 0.033−0.086 mg/100 g DW | Natic *et al*., 2015 |
|  |  | Epicatechin | 8.47−17.12 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Procyanidin B1 | 59.64−224.41 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Procyanidin B2 | 1.02−5.66 mg/100 g DW | Butkhup *et al*., 2013 |
| Phenolic acid | Hydroxycinnamic acid | Chlorogenic acid | 5.3−17.3 mg/100 g DW | Mahmood *et al.,* 2012 |
|  |  | Ferulic acid | 0.057−2.949 mg/100 g DW | Natic *et al*., 2015 |
|  |  | p-Coumaric acid | 0.024−0.142 mg/100 g DW | Natic *et al*., 2015 |
|  |  | o-Coumaric acid | 0.015 mg/g FW | Gundogdu *et al.,* 2011 |
|  |  | Cinnamic acid | 11.64−15.05 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | Caffeic acid | 1.06−8.17 mg/100 g DW | Butkhup *et al*., 2013 |
|  | Benzoic acid | Gallic acid | 7.33−23.34 mg/100 g DW | Butkhup *et al*., 2013 |
|  |  | p-Hydroxybenzoic acid | 0.028−0.154 mg/100 g DW | Natic *et al*., 2015 |
|  |  | Syringic acid | 0.049 mg/g FW | Gundogdu *et al.,* 2011 |
|  |  | Protocatechuic acid | 0.264−0.794mg/ 100 g FW | Natic *et al*., 2015 |
|  |  | Vanillic acid | 0.008 mg/g FW | Gundogdu *et al.,* 2011 |
| MAE: mulberry anthocyanin extract. NA: not available. CMA: crude mulberry anthocyanin. CEE: crude ethanol extract. FW: frozen weight. DW: dry weight. | | | | |

**2.2 Anthocyanins in Mulberry Fruits**

Anthocyanins are water-soluble pigments responsible for the red, purple and black hues of many fruits, including mulberries. In *Morus* species, they represent the most abundant class of polyphenols, especially in darker-colored fruits like *Morus nigra*. These compounds contribute significantly to the antioxidant, anti-inflammatory, and cardioprotective effects of mulberry fruits (Khoo *et al*., 2017).

The predominant anthocyanin identified in mulberries is cyanidin-3-O-glucoside (C3G), which often accounts for more than 60% of total anthocyanin content (Kim & Lee, 2020). Other notable anthocyanins include cyanidin-3-rutinoside, pelargonidin derivatives and delphinidin-3-glucoside. These compounds exhibit strong radical-scavenging activity and inhibit lipid peroxidation, making them effective in mitigating oxidative stress (Dini *et al*., 2019).

Comparative studies have shown that *Morus nigra* fruits contain up to 1,480 mg/kg of total anthocyanins, while *Morus alba* generally has much lower levels, typically below 100 mg/kg (Ozgen *et al*., 2009). The anthocyanin profile is also influenced by factors such as fruit maturity, storage condition, and cultivar genetics. For instance, fully ripe *M. nigra* fruits show nearly twice the anthocyanin content of semi-ripe fruits (Ashtiani *et al*., 2021).

In addition to their antioxidant properties, anthocyanins have been shown to modulate cellular signaling pathways, protect against DNA damage and inhibit inflammatory mediators like cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF-α) (Chen *et al*., 2016). These multifunctional benefits make them key targets in the development of mulberry-based nutraceuticals.

The chemical structures of cyanidin 3-O-glucoside, cyanidin 3-O-rutinoside, pelargonidin 3-O-glucoside and pelargonidin 3-O-rutinoside anthocyanins reported in mulberry fruits are shown in Figure 1 (Khalifa *et al*., 2018).

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**Fig. 1. Chemical structures of representative anthocyanins reported in mulberry fruits.**

**2.3 Flavonoids in Mulberry Fruits**

Flavonoids are an important subclass of polyphenols characterized by their C6–C3–C6 backbone and are widely distributed in fruits and vegetables. In mulberry fruits, especially in *Morus alba*, flavonoids are abundant and contribute significantly to their antioxidant, anti-inflammatory and antidiabetic activities (Butt *et al*., 2008).

The most common flavonoids in mulberries include quercetin, rutin, kaempferol, morin and isoquercitrin. Among them, quercetin and rutin are particularly notable for their strong radical-scavenging activity and ability to chelate metal ions (Katsube *et al*., 2006). Rutin, a glycoside of quercetin, is found in high amounts in *Morus alba* and has been linked to vasoprotective and anti-hyperglycemic effects (Foong *et al*., 2024).

Kaempferol, another flavonol detected in mulberries, has been shown to exert protective effects on cardiovascular and hepatic tissues by modulating oxidative stress pathways and reducing lipid accumulation (Imran *et al*., 2021).

Flavonoid content in mulberries is influenced by cultivar, ripening stage and geographic origin. For instance, Flavonoid contents were reported at 29 and 276 mg Quercetin equivalents/100 g of the fruits of *M. alba* and *M. nigra*, respectively (Abbasi *et al*., 2016). Moreover, recent LC-MS/MS analyses have revealed that white mulberries may contain more diverse flavonol profiles, even though black mulberries dominate in anthocyanin content (Shahzad *et al.,* 2025).

These compounds act synergistically with anthocyanins and phenolic acids, enhancing mulberry’s therapeutic efficacy in conditions such as type 2 diabetes, hypertension and neurodegenerative diseases (Sánchez-Salcedo *et al.,* 2015).

Notable Flavonoids Identified in Mulberry Fruits: Quercetin, Rutin, Kaempferol, Isoquercitrin and Myricetin. These flavonoids have been studied for their antioxidant activity, vascular protection, neuroprotective effects and ability to inhibit enzymes such as α-glucosidase and lipase The chemical structures of quercetin glycosides, kaempferol 3-O-glucoside and quercetin 3-O-rutinoside flavonoids reported in mulberry fruits are shown in Figure 2 (Khalifa *et al.,* 2018).

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**Fig. 2. Chemical structures of representative flavonoids reported in mulberry fruits.**

**2.4 Phenolic Acids in Mulberry Fruits**

Phenolic acids are a major subclass of polyphenols found in mulberry fruits, comprising both hydroxybenzoic acids and hydroxycinnamic acids. These compounds are known for their strong antioxidant capacity and their ability to modulate biological processes relevant to inflammation, metabolic regulation and disease prevention. Among the hydroxybenzoic acids, gallic acid, protocatechuic acid and ellagic acid are commonly found in *Morus alba* and *Morus nigra*. These compounds play a crucial role in inhibiting lipid peroxidation, protecting cellular membranes and inducing apoptosis in abnormal cells (Li *et al*., 2023).

Hydroxycinnamic acids such as chlorogenic acid, caffeic acid, ferulic acid and p-coumaric acid are also prevalent in mulberries. Chlorogenic acid, in particular, has demonstrated antidiabetic, hepatoprotective and anti-obesity effects by regulating glucose metabolism and enhancing insulin sensitivity (Sánchez-Salcedo *et al*., 2015). Its concentration is often highest in black mulberries and tends to increase during fruit ripening.

Mahmood *et al*., 2012 and Gecer *et al*., 2016 observed that chlorogenic acid was the predominant phenolic acid present in mulberry fruits, with concentrations ranging from 5.3 to 17.3 mg per 100 g of dry weight and 2.4 mg per gram, respectively. In contrast, Butkhup *et al*., 2013 identified gallic acid (7.33–23.34 mg/100 g DW) and cinnamic acid (11.64–15.05 mg/100 g DW) as the primary phenolic acids found in different mulberry cultivars.

Overall, there is considerable variation in the types and levels of polyphenolic compounds reported in mulberry fruits across different research. These inconsistencies can be attributed to several factors, including the specific variety of mulberry studied, the methods used for extraction and analysis, genetic variability and agronomic conditions such as climate, humidity, light exposure and the ripening stage of the fruit (Butkhup *et al*., 2013;Natic, *et al*., 2015).

Moreover, several studies suggest synergistic interactions between phenolic acids and other polyphenols (like flavonoids), which enhance their therapeutic efficacy in chronic conditions such as diabetes, cancer and cardiovascular disease (Iqbal *et al*., 2022).

The chemical structures of the phenolic acids—protocatechuic acid, caffeic acid, vanillic acid and chlorogenic acid reported in mulberry fruits are shown in Figure 3 (Khalifa *et al.,* 2018).

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**Fig. 3. Chemical structures of representative phenolic acids reported in mulberry fruits.**

**2.5 Factors Affecting Polyphenol Content in Mulberries**

The polyphenolic composition of mulberry fruits is highly variable and influenced by several genetic, environmental and postharvest factors. Understanding these variations is essential to standardize mulberry-based health products and to identify cultivars with superior nutraceutical properties.

**1. Species and Genotypic Variation**

Different *Morus* species and cultivars exhibit significant differences in polyphenol profiles. Morus nigra typically contains higher levels of anthocyanins and total phenolic content than Morus alba, which is often richer in flavonoids like rutin and quercetin (Ercisli & Orhan, 2007). Within each species, genetic diversity further contributes to variations in compound concentration and bioactivity (Shahzadi *et al*., 2025).

Skrovankova *et al.* (2022) studied the diversity of phytochemical and antioxidant characteristics of black mulberry (*Morus nigra* L.) fruits from Turkey. Significant differences in phytochemical and antioxidant properties were observed among the analyzed *M. nigra* genotypes. Based on the highest values of these traits, three *M. nigra* genotypes were identified as the most promising and are recommended for fruit production. These results highlight the potential for utilizing local black mulberry genotypes in crop selection and breeding programs.

**2. Maturity and Ripening Stage**

The ripening stage has a profound effect on the accumulation of polyphenols in mulberry fruits. Several studies have reported a gradual increase in total phenolics, especially anthocyanins, during the fruit maturation process (Mahmood *et al.,* 2017). Cyanidin derivatives, in particular, increase significantly in fully ripened black mulberries compared to immature stages.

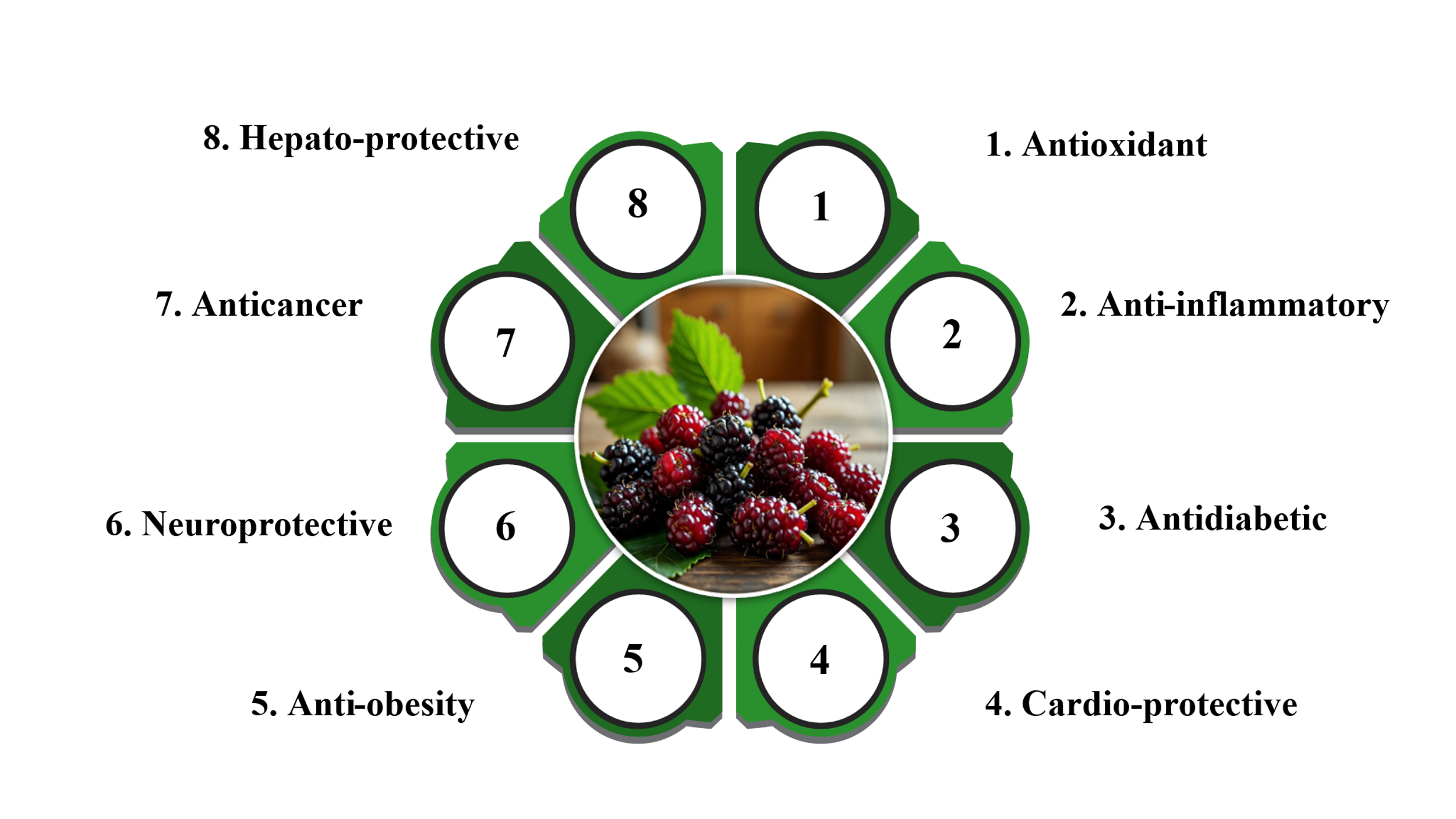
In contrast, some phenolic acids, such as gallic acid p-hydroxybenzoic acid, chlorogenic acid, p-coumaric acid and sinapic acid  may decrease slightly upon full ripening, possibly due to their conversion into other derivatives (Saensouk *et al*., 2022). Therefore, harvesting time is a critical factor in optimizing polyphenol yield.

**3. Environmental Conditions**

Environmental factors such as altitude, temperature, sunlight exposure and soil composition have a profound influence on the biosynthesis and accumulation of polyphenols in mulberry fruits. According to Zhang *et al.* (2023), variations in cultivation conditions can significantly alter the phenological stages, yield and concentration of bioactive compounds, including polyphenols, in different mulberry cultivars. For instance, mulberries grown under higher sunlight exposure or in specific soil types may exhibit enhanced levels of flavonoids and anthocyanins, contributing to their antioxidant potential. These environmental cues modulate physiological processes, leading to dynamic changes in the synthesis of secondary metabolites like polyphenols. Therefore, optimizing cultivation practices according to local environmental factors is crucial for improving the nutritional and functional quality of mulberry fruits.

**4. Postharvest Handling and Storage**

Postharvest factors such as storage temperature, duration and processing methods critically influence the stability and preservation of polyphenols in mulberry fruits, especially anthocyanins. As highlighted by Yavaş *et al*. (2023), anthocyanins are particularly vulnerable to environmental stresses like oxidation, elevated temperatures and fluctuations in pH, which can lead to rapid degradation and loss of their antioxidant efficacy. Their study on black mulberry (*Morus nigra* L.) concentrate revealed that prolonged storage, especially at higher temperatures, resulted in significant reductions in anthocyanin content and overall antioxidant capacity. Additionally, the physical and chemical properties of the concentrate, including color and total phenolic content, deteriorated over time. These findings underscore the importance of maintaining low storage temperatures and minimizing exposure to light and oxygen to retain the polyphenolic integrity of mulberry products.



**Figure 4. Schematic overview of biological activities of mulberry fruit**

**3. Health Benefits of Mulberry Polyphenols**

As shown in Figure 4, mulberry-derived polyphenols exert pleiotropic bioactivities, including antioxidant defense, metabolic regulation, neuroprotection and cytoprotective effects, underscoring their potential as multifunctional therapeutic agents.

**3.1 Antioxidant Activity**

**3. Health Benefits of Mulberry Polyphenols**

Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, plays a central role in the development of chronic diseases such as cancer, cardiovascular disorders, diabetes and neurodegeneration (Halliwell & Gutteridge, 2015). Mulberry fruits are rich in polyphenols particularly anthocyanins, flavonoids and phenolic acids that contribute significantly to their antioxidant activity through multiple mechanisms.

**Mechanisms of Antioxidant Action**

Mulberry-derived polyphenols exhibit antioxidant effects primarily *via*:

* Direct scavenging of free radicals such as hydroxyl and superoxide anions
* Chelation of metal ions that catalyze ROS formation
* Inhibition of lipid peroxidation
* Upregulation of endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) (Katsube *et al*., 2006)

Anthocyanins, particularly cyanidin-3-O-glucoside (C3G), are potent radical scavengers and have been shown to inhibit DNA damage and lipid peroxidation *in vitro* and in animal models (Khoo *et* *al*., 2017; Chen *et al*., 2006). Similarly, flavonoids such as rutin can protect biomolecules from oxidative damage by modulating oxidative enzyme expression (Pandey *et al*., 2021).

Dou *et al*. (2022) demonstrated that mulberry fruits release significant amounts of phenolic compounds during *in vitro* digestion, contributing to strong antioxidant activity. These antioxidants were positively correlated with α-glucosidase inhibition, indicating potential benefits for glycemic control. Additionally, fermentation of undigested fractions promoted gut health by producing SCFAs and modulating intestinal flora. Another study by Katsube *et al.* (2006) reported that *M. alba* extracts exhibited high radical-scavenging activity in DPPH and ABTS assays. The antioxidant capacity correlated strongly with total phenolic content (R² > 0.9).

The flavonoid ethanol extract from mulberry fruit (FEM), obtained at a concentration of 53 mg/g from fresh fruit, demonstrated strong antioxidant activity, particularly in DPPH radical scavenging and reducing power assays. FEM significantly inhibited H₂O₂-induced red blood cell hemolysis in a dose- and time-dependent manner. Additionally, it effectively suppressed lipid peroxidation in the liver, mitochondria and microsomes (Raman *et al.,* 2016).

**3.2 Anti-inflammatory Potential of Mulberry Polyphenols**

Chronic inflammation plays a fundamental role in the progression of many non-communicable diseases such as atherosclerosis, type 2 diabetes, rheumatoid arthritis and neurodegenerative disorders. Mulberry-derived polyphenols, particularly flavonoids and anthocyanins, have demonstrated strong anti-inflammatory potential in vitro and in vivo through modulation of inflammatory signaling pathways and suppression of pro-inflammatory mediators (Chen *et al*., 2025).

**Key Mechanisms of Anti-inflammatory Action**

Mulberry polyphenols exert anti-inflammatory effects through:

* Inhibition of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β)
* Downregulation of nuclear factor-kappa B (NF-κB), a master regulator of inflammation
* Suppression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS)
* Inhibition of MAPK signaling, reducing expression of inflammation-related genes

In human macrophages, cyanidin-3-glucoside has been shown to suppress the production of TNF-α and IL-6 by inhibiting NF-κB nuclear translocation (Dini *et al*., 2019). Similarly, quercetin and rutin inhibit COX-2 expression and reduce nitric oxide (NO) production, thereby attenuating acute and chronic inflammation (Lee *et al*., 2024).

The anthocyanins in *M. nigra* fruit are reported to have anti-inflammatory activity. C3G and C3R exert anti-inflammatory effects through the inhibition of pro-inflammatory cytokines in xylene-induced ear edema and carrageenan-induced foot edema in mice (Chen *et al*., 2016).

The pain-relieving properties of fruit extracts from *Morus nigra*, *Morus mongolica* and *Morus alba* were observed in Kunming strain mice. The anthocyanin cyanidin-3-O-glucoside (C3G) and flavonoids rutin (Ru) and isoquercetin (IQ) abundantly present in Morus nigra were identified as the principal bioactive compounds involved in this effect. These constituents contributed to a notable decrease in the pro-inflammatory cytokine interleukin-6 (IL-6), suppression of inducible nitric oxide synthase (iNOS) production and enhancement of the anti-inflammatory cytokine interleukin-10 (IL-10). These inflammatory mediators are strongly associated with pain signaling and modulation (Chen *et al*., 2017)

In LPS-stimulated RAW 264.7 macrophages, cyanidin-3-glucoside inhibited iNOS and COX-2 mRNA expression and prevented nuclear translocation of NF-κB p65, indicating transcriptional regulation of inflammation (Dini *et al*., 2019).

**3.3 Antidiabetic Effects of Mulberry Polyphenols**

Diabetes mellitus, particularly type 2 diabetes, is a chronic metabolic disorder characterized by high blood sugar levels due to insulin resistance or inadequate insulin production. Polyphenol-rich mulberry fruits have gained significant attention for their natural blood glucose-lowering effects and their potential as functional food supplements for diabetic individuals (Rodrigues *et al*., 2019).

Several animal studies have demonstrated that mulberry fruit extracts can help lower fasting blood glucose, improve glucose tolerance and reduce insulin resistance. For example, diabetic rats treated with *Morus alba* fruit extract showed significant reductions in blood glucose levels, along with improvements in lipid profiles and body weight (Tornaghi *et al.,* 2023). These effects were linked to the high content of polyphenols like quercetin, rutin and chlorogenic acid, which help regulate carbohydrate digestion and absorption.

Choi *et al.* (2016) demonstrated that mulberry fruit extract (MFE) significantly improved insulin sensitivity and reduced blood glucose and HbA1c levels in type 2 diabetic mice. MFE enhanced GLUT4 expression in skeletal muscle through activation of AMPK and AS160 pathways, while also suppressing hepatic gluconeogenesis. These findings suggest that MFE may serve as a promising natural therapeutic agent for managing hyperglycemia in type 2 diabetes.

Yan and Zheng (2017) reported that mulberry anthocyanin extract (MAE) alleviated oxidative stress and improved insulin sensitivity in high-glucose-exposed HepG2 cells and type 2 diabetic mice. MAE activated the AMPK/ACC/mTOR signaling pathway, enhanced glucose uptake and reduced pancreatic injury, highlighting its potential in managing oxidative damage and metabolic dysfunction in diabetes..

In clinical studies, supplementation with mulberry powder or capsules has shown modest but consistent improvements in post-meal blood sugar control. A study by Andallu *et al*. (2001) reported that type 2 diabetic patients who consumed 10 g of dried *M. alba* fruit powder daily for 3 months experienced:

* A significant reduction in fasting and postprandial glucose levels
* Improved HbA1c values (long-term blood sugar control)
* Better lipid profiles (reduced total cholesterol and LDL)

These outcomes suggest that mulberry fruits can serve as natural adjuncts to conventional diabetes treatment, especially for people with mild to moderate hyperglycemia.

Hoogenraad *et al.* (2025) demonstrated in a placebo-controlled human trial that mulberry fruit extract (MFE), rich in 1-deoxynojirimycin (DNJ), significantly reduced postprandial blood glucose and insulin responses after carbohydrate-rich meals. While DNJ was the primary active compound, the enhanced efficacy of MFE suggests a synergistic role of other bioactives, including polyphenols. These findings support the potential of MFE as a natural supplement for improving glycemic control in humans.

**3.4 Cardiovascular Benefits of Mulberry Polyphenols**

Cardiovascular diseases (CVDs) remain one of the leading causes of mortality globally and diet plays a critical role in both prevention and management. Polyphenols from mulberry fruits have been shown to support heart and vascular health through their ability to improve lipid profiles, reduce blood pressure and enhance blood vessel function (Zhang *et al*., 2018).

Yang *et al*. (2010) found that rats fed a high-fat diet supplemented with 5% or 10% mulberry fruit powder exhibited a significant reduction in serum and hepatic triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol levels. Additionally, a notable elevation in high-density lipoprotein (HDL) cholesterol was observed in the mulberry-supplemented groups. The study suggested that the rich dietary fiber content in mulberry fruits may suppress liver fat synthesis and enhance LDL receptor activity. Furthermore, the hypolipidemic potential of mulberry fruits was attributed to their abundant dietary fiber and linoleic acid content.

Chen *et al*, (2005) reported that New Zealand white rabbits fed a high-cholesterol diet (HCD) composed of 95.7% standard Purina chow, 3% lard oil and 1.3% cholesterol, along with 0.5% or 1.0% aqueous extract of mulberry fruits for 10 weeks, exhibited significantly reduced levels of total cholesterol, LDL cholesterol and triglycerides compared to those receiving only the HCD. The study also demonstrated that supplementation with mulberry fruit extract led to a substantial reduction (42–63%) in the severity of atherosclerotic lesions in the aorta, as confirmed by histopathological analysis of vascular tissues. Additionally, the cholesterol-lowering effect of the mulberry extract appeared to be dose-responsive. Importantly, no adverse effects on liver or kidney function were observed in rabbits receiving the mulberry extract alongside the high-cholesterol diet.

Several studies have reported that regular intake of mulberry extracts or juice helps reduce total cholesterol, low-density lipoprotein (LDL) and triglyceride levels, while raising beneficial high-density lipoprotein (HDL) cholesterol (Yang & Zheng, 2010). These changes are particularly relevant for individuals at risk of atherosclerosis and coronary artery disease.

In a randomized controlled trial involving 58 adults aged 30–60 years with elevated cholesterol levels, Sirikanchanarod *et al*. (2016) found that daily intake of 45 g of freeze-dried mulberry fruit (providing 325 mg of anthocyanins) over six weeks significantly reduced total cholesterol and LDL levels compared to the control group (both p < 0.001). The researchers suggested that mulberry fruit could serve as a natural alternative for managing hypercholesterolemia. Consequently, regular consumption of mulberry fruit may help lower the risk of atherosclerosis, owing to its lipid-lowering and antioxidant properties that protect against LDL oxidation.

Chan *et al*. (2015) investigated the anti-atherosclerotic potential of mulberry polyphenol extracts (MPEs) in vascular smooth muscle cells (VSMCs) and found that MPEs inhibited VSMC proliferation and migration key contributors to atherosclerosis. The extracts induced nitric oxide (NO) production and activated the AMPK/p53 signaling pathway, leading to G0/G1 cell cycle arrest. This effect was attributed to active compounds such as rutin, protocatechuic acid, epigallocatechin gallate (EGCG), caffeic acid and naringenin. Their findings suggest that MPEs may help prevent atherosclerosis by modulating VSMC behavior through oxidative and signaling pathways.

**3.5 Anti-obesity and Metabolic Health Benefits of Mulberry Polyphenols**

Obesity is a key risk factor for many chronic diseases, including type 2 diabetes, heart disease and metabolic syndrome. Mulberry polyphenols have attracted attention for their ability to support healthy weight management, regulate fat metabolism and improve energy utilization making them promising components in anti-obesity diets (Boccellino & Angelo, 2020).

Chatturong *et al*. (2021) demonstrated that dried mulberry fruit powder (DMP) significantly reduced body weight, food intake, visceral fat accumulation and liver lipid levels in high-fat diet-fed mice. Both low and high doses of DMP improved liver total cholesterol, while only the higher dose reduced triglycerides, indicating a dose-dependent effect. These findings suggest that natural, unprocessed mulberry fruit possesses anti-obesity and hepatoprotective properties, supporting its potential use as a cost-effective dietary supplement for weight.

The ethanolic extract of *Morus nigra* fruits improved the hepatic steatosis induced by a hyperlipid diet in C57BL/6J mice by a significant reduction in the presence of lipid droplets in hepatocytes and a decrease in serum levels of ALT and AST and liver levels of triglycerides and total cholesterol. In addition, the protective effects of the extract were associated with improved glucose tolerance, insulin resistance and insulin sensitivity, as well as induction of fatty acid oxidation and decreased fatty acid and cholesterol biosynthesis (Song *et al*., 2016).

In a high-fat diet-induced obesity model, the combined administration of mulberry leaf extract (MLE) and mulberry fruit extract (MFE) demonstrated significant anti-obesity potential. Mice treated with the high-dose combination (333 mg/kg/day MLE and 167 mg/kg/day MFE) for 12 weeks exhibited reduced body weight gain, plasma triglyceride levels, adipocyte size and hepatic steatosis compared to the high-fat control group. Importantly, this combinational treatment also improved insulin sensitivity and glucose tolerance without inducing hepatic toxicity. The anti-obesity effects were linked to decreased oxidative stress and inflammatory responses, as evidenced by the reduced expression of manganese superoxide dismutase, inducible nitric oxide synthase, C-reactive protein, monocyte chemoattractant protein-1, TNF-α and IL-1 in liver and adipose tissues. These findings suggest that the synergistic action of mulberry fruit and leaf extracts can effectively counteract obesity by attenuating lipid accumulation, inflammation and oxidative stress (Lim *et al*., 2013).

Mulberry fruit water extract (MWE) demonstrated significant anti-obesity effects in high-fat diet-induced obese male hamsters. After 12 weeks of supplementation, MWE reduced body weight gain and visceral fat accumulation. These effects were accompanied by decreases in serum triglycerides, cholesterol, free fatty acids and LDL/HDL ratio. Mechanistically, MWE downregulated hepatic fatty acid synthase and HMG-CoA reductase while upregulating peroxisome proliferator-activated receptor α (PPAR-α) and carnitine palmitoyltransferase-1 (CPT-1), indicating modulation of lipogenesis and lipolysis. No adverse physiological effects were observed, supporting MWE as a safe and effective agent for managing obesity through regulation of lipid metabolism (Peng *et al*., 2021).

Although human trials are limited, some early studies suggest that mulberry-based dietary supplements, when combined with lifestyle modifications, can support weight management. Parklak *et al*. (2024) found that daily consumption of a concentrated mulberry drink (CMD) from the Kamphaeng Saen cultivar significantly improved metabolic markers in obese individuals. CMD intake reduced systolic and diastolic blood pressure, triglyceride levels, fasting plasma glucose and C-reactive protein, indicating both cardiometabolic and anti-inflammatory benefits. These results suggest CMD may serve as a functional beverage for managing metabolic syndrome in obesity.

**3.6 Neuroprotective and Cognitive Health Effects of Mulberry Polyphenols**

Cognitive decline, memory impairment and neurodegenerative diseases such as Alzheimer’s and Parkinson’s are rising globally with increasing life expectancy. Recent research has highlighted the potential of mulberry polyphenols, particularly anthocyanins, flavonoids and phenolic acids, in supporting brain health and protecting against age-related cognitive decline. (Norouzkhani *et al.*, 2024).

Animal studies suggest that mulberry polyphenols can improve learning, memory and attention in rodents exposed to stress, aging, or chemical-induced cognitive impairment. In a study by Azab (2025), aged mice treated with mulberry fruit extract showed significant improvements in spatial memory and learning performance in maze tests. These cognitive benefits were linked to the antioxidant and anti-fatigue properties of anthocyanins and flavonoids.

Similarly, administration of *Morus nigra* fruit extract in mice helped maintain memory function and reduced signs of brain oxidative damage induced by stress or a high-fat diet (Turgut *et al.*, 2016).

Kang *et al.* (2006) demonstrated that cyanidin-3-O-β-D-glucopyranoside (C3G), a key anthocyanin isolated from mulberry fruit extracts, exhibits significant neuroprotective potential. In their study, a 1% HCl methanol extract of mulberry fruits showed a cytoprotective effect on PC12 neuronal cells exposed to hydrogen peroxide, indicating antioxidant activity against oxidative stress. Moreover, the extract effectively attenuated cerebral ischemic damage induced by oxygen-glucose deprivation (OGD) *in vitro*. The neuroprotective efficacy of C3G was further validated *in vivo* using a mouse model of transient middle cerebral artery occlusion (MCAO), where treatment significantly reduced ischemic injury compared to control. These findings suggest that mulberry fruits, through their rich content of polyphenols such as C3G, may offer therapeutic benefits in mitigating neuronal damage associated with ischemia and oxidative stress, thus supporting their potential use in the prevention or management of neurodegenerative disorders.

Shin *et al*. (2021) investigated the neuroprotective potential of mulberry fruit extract (MFE) against oxidative stress-induced neuronal damage and memory impairment. Using glutamate-exposed HT-22 hippocampal cells and a scopolamine-induced memory-deficit mouse model, they found that MFE improved cell viability, enhanced glutathione levels, reduced ROS accumulation and modulated apoptosis-related proteins. Notably, MFE activated the TrkB/Akt/CREB/BDNF signaling pathway and antioxidant responses *via* Nrf2 translocation. *In vivo*, MFE ameliorated cognitive deficits by restoring cholinergic function and protecting hippocampal neurons. These findings suggest that MFE, rich in polyphenols, may be a promising nutraceutical for preventing memory loss in neurodegenerative diseases.

Oz *et al*. (2024) explored the potential benefits of black mulberry (*Morus nigra*) on cognitive performance in elderly individuals with mild-to-moderate Alzheimer’s disease (AD). In this 12-week trial, 20 participants received 20 g/day of black mulberry concentrate, while 19 served as a non-intervention control group. Cognitive assessments using MMSE and ADAS-Cog, along with mood evaluation through GDS-15, revealed that the control group experienced a decline in MMSE scores and increased depressive symptoms. Conversely, the intervention group maintained stable MMSE scores and showed significant improvement in ADAS-Cog (p = 0.002). These findings suggest that black mulberry may help preserve cognitive function in AD patients, potentially due to its antioxidant or iron-rich composition. Additional research with larger cohorts is recommended to validate its role as a safe, accessible dietary option for mitigating cognitive decline.

Casedas *et al*. (2024) evaluated the neuroprotective effects of a solvent-free, polyphenol-rich black mulberry (*Morus nigra* L.) extract using both in vitro (Neuro-2a cell line) and in vivo (Caenorhabditis elegans) models. The extract significantly reduced hydrogen peroxide-induced intracellular ROS levels and improved cell viability, indicating cytoprotective and antioxidant activity. In C. elegans, the extract mitigated β-amyloid-induced neurotoxicity in the CL4176 Alzheimer’s disease model. Additionally, it moderately inhibited monoamine oxidase A (MAO-A), suggesting potential for mood regulation and neuroprotection. Overall, the findings support the role of *M. nigra* as a functional food with neuroprotective benefits relevant to neurodegenerative disorders.

**3.7 Anticancer Potential of Mulberry Polyphenols**

Cancer remains one of the most pressing global health challenges. Dietary antioxidants and polyphenols from natural sources have been extensively studied for their role in reducing cancer risk and supporting general cellular health. Mulberry fruits, particularly those rich in anthocyanins, flavonoids and phenolic acids, have shown promising results in inhibiting cancer cell growth and protecting normal cells from damage.

**Cell-Protective and Anti-Proliferative Effects**

Several laboratory studies have demonstrated that mulberry polyphenol extracts can:

* Inhibit the growth and spread of abnormal cells
* Prevent oxidative damage to DNA
* Support natural cell repair processes
* Reduce mutation rates in stressed cells

For example, Chen *et al*. (2006) reported that anthocyanin-rich extracts from mulberry significantly reduced the growth of human cancer cells *in vitro*, including those from lung, liver and colon origins. These effects were linked to the antioxidant and detoxifying properties of polyphenols, which help maintain the integrity of healthy tissues.

Sargara *et al*.( 2025) evaluated the anticancer properties of *Morus alba* L. fruit extracts at two maturity stages young (MAF-Y) and ripe (MAF-R) against human lung adenocarcinoma (A549) cells. Both extracts exhibited significant cytotoxicity, with MAF-R showing a lower IC50 value (18.4 ± 3.01 µg/mL) than MAF-Y (29.41 ± 3.6 µg/mL), indicating higher potency. Phytochemical analysis revealed higher phenolic content and antioxidant activity in the ripe extract. Both extracts inhibited cell migration and induced apoptosis through a ROS-dependent mechanism, disrupting mitochondrial membrane potential and causing DNA fragmentation. These findings highlight the therapeutic potential of *M. alba* fruit extracts as natural anticancer agents targeting lung carcinoma cells.

Flavonoid-rich extracts obtained from black mulberry wine residues (BMWR-E) showed notable antioxidant and anticancer activities under optimized ultrasound-assisted enzymatic extraction conditions, yielding 5.672 mg/g of extract. The extract exhibited significant DPPH, hydroxyl and superoxide radical scavenging activity. At concentrations ≥0.2 mg/mL, BMWR-E induced apoptosis in HepG2 liver cancer cells by upregulating Bax, caspase-3 and caspase-12, while downregulating Bcl-2 and arresting the cell cycle at the G0/G1 phase. Importantly, it exhibited no cytotoxicity to normal BRL-3A cells, highlighting its selectivity. These findings underscore the potential of black mulberry wine residues as a valuable source of natural antioxidants and anticancer agents (Ma *et al*., 2024).

In relation to anticancer effects on colon tissue, lyophilized aqueous extracts of black mulberry (Morus nigra) have been explored for their bioactivity. The fruit extracts were derived using a 75% (v/v) ethanol–water solvent system under both thermally assisted and non-heated conditions. Importantly, extracts obtained through heated extraction exhibited enhanced biological efficacy compared to those prepared without heat application. These preparations significantly suppressed cell proliferation, induced morphological deviations in cancer cells, elevated intracellular calcium ion (Ca²⁺) levels, disrupted mitochondrial membrane integrity and promoted the accumulation of reactive oxygen species (ROS) (Cui *et al*., 2020). Modifying ROS concentrations within the tumor microenvironment represents a crucial strategy for tipping the balance between cellular survival and programmed cell death. Increasing oxidative stress may activate apoptosis or autophagy pathways in malignant cells (Ferraz *et al.,* 2020). *M. nigra* is widely recognized for its robust antioxidant potential, attributed to its abundance of polyphenolic and anthocyanin compounds (Hassimotto *et al*., 2007; Singh *et al*., 2019; Issa & Abd-Aljabar, 2013), positioning it as a valuable phytotherapeutic agent for regulating redox signaling and associated pathways in cancer treatment.

Dalkılıç *et al*. (2021) investigated the cytotoxic effects of black mulberry (*Morus nigra* L.) fruit extract on human breast (MDA-MB-231) and prostate (PC3) cancer cell lines. Using various concentrations (1–10% v/v) over a 72-hour incubation period, cell viability was assessed via MTT assay. The extract exhibited a dose-dependent cytotoxic response, showing significant inhibition of cell viability at 10% concentration, particularly in breast cancer cells, suggesting *M. nigra*’s potential as a natural anticancer agent.

**Preventive Role in Diet**

Although human cancer treatment requires clinical care, polyphenol-rich foods like mulberry may support the body's natural defenses. By reducing oxidative stress, inflammation and cell damage, these compounds contribute to cancer prevention strategies when consumed as part of a healthy diet. Mulberries may also enhance the effects of other protective nutrients, making them ideal for inclusion in functional foods, cancer-prevention supplements and wellness programs.

**Reported Anticancer Benefits:**

* Reduced abnormal cell growth in lab studies
* Less DNA damage in stressed cells
* Protection against cancer-inducing agents in animal models
* Supportive role in overall cellular health and detoxification

**3.8 Additional Health Benefits and Functional Applications**

Beyond its well-documented antioxidant, anti-atherosclerotic, immunoregulatory, anticancer, antihyperglycemic, lipid-lowering and neuroprotective effects, mulberry fruit has also demonstrated several other pharmacological benefits. The hepatoprotective properties of mulberry water extract (MWE) were assessed in mice with chemically induced liver damage, revealing that MWE significantly mitigated hepatic injury. This effect was primarily attributed to the suppression of lipogenesis, attenuation of oxidative stress and inflammation, enhancement of fatty acid transport and stimulation of β-oxidation pathways (Tang *et al*., 2013). The anti-fatigue potential of purified mulberry juice (MJP) and mulberry pomace (MMP) was analyzed using a weight-loaded swimming endurance test, where both extracts extended the swimming duration, with MMP showing a more pronounced effect than MJP (Jiang *et al*, 2013). The influence of a combined mulberry leaf and fruit extract (MLFE) on early-stage skin wound repair in obese mice was also explored, suggesting that MLFE accelerates delayed wound healing by activating the NLRP3 inflammasome signaling pathway (Eo & Lim, 2016). Khan & Jain (2016) demonstrated that ethanolic extract of mulberry fruit possesses significant gastroprotective properties in rats, possibly through its antioxidant-mediated mechanisms. Moreover, the potential of astragalin (kaempferol-3-O-glucoside), a bioactive compound isolated from mulberry fruit, to alleviate menopausal symptoms was examined in both cell and animal models. Findings revealed that astragalin can suppress granulosa cell apoptosis, stimulate the production of 17β-estradiol and progesterone and enhance levels of follicle-stimulating hormone and luteinizing hormone (Wei *et al*., 2016).

**4. Toxicity and Safety Assessment of Mulberry Fruit**

Despite being derived from plants and often regarded as “natural,” herbal remedies are not inherently free from adverse effects. Several studies have documented negative side effects linked to herbal usage (Ernst, 1998; Eddy, 2005; Jordan *et al*., 2010; Bent *et al*., 2004; Stickel *et al*., 2000). Mulberry fruit (*Morus* spp.), traditionally consumed both as a dietary component and medicinal agent, has attracted scientific attention due to its broad spectrum of bioactivities. These therapeutic attributes position mulberry as a promising candidate for the formulation of functional foods and phytopharmaceuticals, especially in response to growing consumer interest in health-promoting products. Consequently, thorough evaluation of its safety profile is essential.

Peng *et al.* (2011) assessed both the anti-obesity efficacy and safety of mulberry water extract (MWE) through oral administration (0.5%–2%, w/w) over a 12-week period in hamsters. The results demonstrated not only favorable anti-obesity effects but also confirmed the absence of toxicity in vivo. Similarly, Chang et al. (2016) conducted subchronic oral toxicity and genotoxicity studies on mulberry fruit extract (MFE) using Sprague–Dawley rats administered with daily oral doses of 40, 200 and 1000 mg/kg for 90 days. No mortality or abnormal clinical symptoms were observed and parameters such as food and water intake, body and organ weights and hematological or biochemical indices remained unaffected. Furthermore, the extract did not exhibit any mutagenic potential in Salmonella typhimurium strains TA98, TA102 and TA1535. In human health risk assessments, mulberry fruit consumption showed no measurable carcinogenic or non-carcinogenic threats to adult consumers, supporting its classification as a safe dietary source (Abbasi *et al*., 2016).

**5. Conclusion**

Mulberry fruits, particularly those from *Morus alba* and *Morus nigra*, are rich in polyphenolic compounds such as anthocyanins, flavonoids and phenolic acids, which have shown considerable promise in promoting human health. Numerous studies have demonstrated their physiological benefits, including antioxidant and anti-inflammatory effects, blood glucose and lipid regulation, cognitive enhancement, immune support and potential anticancer activity. These effects, observed through both experimental and clinical evidence, support the integration of mulberry polyphenols into daily diets and functional food systems aimed at disease prevention and health maintenance. Despite the growing body of research, further work is needed to standardize mulberry-based products and validate their long-term efficacy in human populations. Variations in polyphenol content due to species, maturity and processing methods require careful evaluation. Additionally, improved delivery formats could enhance the bioavailability of these compounds. Overall, mulberries stand out as a promising and accessible natural resource for functional nutrition and their broader application in health promotion strategies should be encouraged through continued scientific exploration.

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