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Medicinal values of mulberry (*Morus* spp.): A review

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Abstract
The phytochemical composition of mulberry and their positive impacts on human health, such as their antioxidant, anticancer, anti-diabetic, and immune-modulating properties, have given them a unique significance in recent years. Fruits, leaves, twigs, and roots of *Morus* spp. are believed to be rich sources of secondary metabolites, such as flavonoids, anthocyanins, and alkaloids. Black mulberry berries also contain flavonols and phenolic acids in addition to anthocyanins (mostly cyanidin-3-O-glucoside). The mulberry leaves are a significant source of flavonols, particularly chlorogenic acid, which is the main phenolic acid, as well as quercetin and kaempferol in their glycosylated forms. The roots, barks and twigs of mulberry trees contain prenylated flavonoids, primarily morusin. The health benefits of mulberry include their ability to enhance digestion, lower cholesterol, aids in weight loss, promote blood circulation, strengthen bone structures, and improve immunity. The mulberry fruit's potential health benefits include slowed ageing, decreased arterial pressure, eye protection, and enhanced body metabolism.

Keywords: Mulberry; antioxidants; health benefits; flavonoids; anthocyanins; anticancer; anti-diabetic

1. Introduction
The genus *Morus* and family Moraceae include the perennial and woody mulberry, which is indigenous to China. Mulberry plants, a deciduous plant that thrives in a variety of climates, including tropical, subtropical, and temperate, exhibit rapid growth and a brief period of propagation. Because of its chemical makeup and pharmacological action, mulberry plants have been utilised for ages in agriculture, food, cosmetics, and medicine. The oldest and most effective treatments for human illness are herbal medicines. As people study and test more natural, effective treatments that have been used for many generations, their faith in these treatments is strengthening. Almost 80% of people worldwide still utilise natural remedies, many of which are made from plants like mulberry, according to the World Health Organization.
This study, which is based on contemporary mulberry literature, aims to examine the efficacy of mulberry as a whole plant by emphasizing the phytochemical profile information of every botanical part of the *Morus* tree and assigning every part to various functional qualities while also investigating its medical uses for nutraceuticals.

2. Nutritional values of the botanical parts of *Morus* spp
The *Morus* tree is a renowned medicinal plant. The fruits, leaves, twigs, and bark of this plant have all been employed in traditional Chinese and Indian medicine because of their unique effects on the human body.

2.1 Mulberry fruits
Several *Morus* sp. fruits (approximately 2 to 3 cm long) form collectively and are aligned lengthwise along the central axis, resembling blackberries. They are low in calories but high in minerals and antioxidants, ensuring general excellent health. Around 70% of the fruits are made up of water, and each species pH levels vary. The species, fruit maturity, soil type, and environmental factors all affect the mineral content of mulberry fruits. Ten elements, with potassium predominating, were identified in Turkish mulberry fruits in the study by Ercisli and Orhan, 2007 [1]. The amount of iron in *M. alba* and *M. nigra*, an essential mineral that is quite uncommon in berry fruits, is high at 4.2 mg/100g. N, K, and P are discovered in high concentrations in another research [2] of the macroelements, however sodium is detected in very low concentrations (0.01 mg) in *M. alba* and *M. nigra* cultivated in Spain. In *M. alba* and *M. nigra*, respectively, the amounts of iron ranged from 28.20 to 46.74 mg/kg and 23.92

to 37.09 mg/kg, indicating good sources of non-heme iron. The highest amounts of minerals were found in the black mulberry, which was cultivated in Western Serbia at various heights, with a notable variance depending on altitude. Because of the mulberry's high vitamin C and iron content, iron has a better bioavailability and can be utilised to treat anaemia [3]. Linoleic acid predominates when it comes to the fatty acid profile of mulberry fruits, followed by palmitic acid and oleic acid, the latter of which is only found in *M. alba* and *M. nigra* [4]. The nutrients in mulberry fruits are outlined in Figure 1 and are extremely significant to human metabolism. White sap is present in unripe mulberries, or the green portions of the fruits, and it may be poisonous, stimulating, or moderately hallucinatory [5].

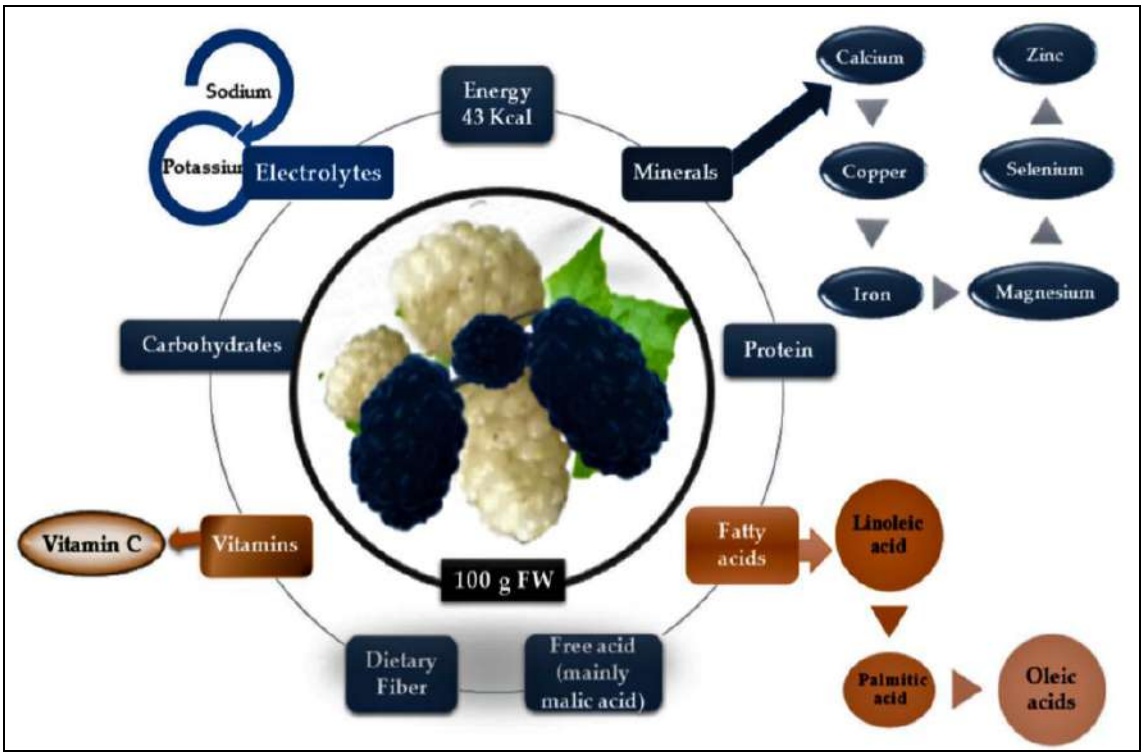

Fig 1: The nutrients present in mulberry fruits

2.2 *Morus* leaves

In addition to being the sole known food source for the growth of silkworms (*Bombyx mori*), mulberry leaves are just as valuable as the fruits since they also contain bioactive molecules, vitamins, organic acids, minerals, and proteins. The iron content of *M. alba* and *M. nigra* leaves is substantial (119.3–241.8 mg/kg), while the concentrations of the other minerals are relatively low. Ca was discovered to be the most prevalent macronutrient, followed by N, K, and Mg [6]. Mulberry leaves have been found to improve the carcass' development and finishing performance, the meat's nutritional quality, the muscles chemical makeup, the thickness of back fat, the muscles fat deposition, the amounts of crude protein and amino acids in the muscles, and more [7].

2.3 Mulberry twig and root bark

Mulberry twigs are utilised in medicine and include compounds like arabinosides, glucose, fructose, maltose, stachyose, and tannin that have a number of positive benefits on serious illnesses that impact the human body [8]. Bioactive substances were discovered, although there is currently no information on the concentration of minerals, carbohydrates, lipids, or root bark proteins.

3. *Morus* species botanical part's phytochemical composition

Flavonoids are the most prevalent phytochemicals in *Morus* species. Table 1 offers updated data on the screening of phytochemical content discovered in both the fruits as well as leaves of *Morus* sp. from the literature of the most recent years (2016–2021). Flavonoids offer a remarkable range of biological actions and are found in great proportions in the epidermis of leaves, fruit skin, and bark.

Table 1: Polyphenol, anthocyanin, and flavonoid levels in mulberry fruits and leaves

Species	Organs	Total Polyphenols	Anthocyanins	Flavonoids	References
Morus nigra	Fruits	502.43±5.10 mg GAE/ 100 g fw	81.36±2.05 mg C3GE/ 100 g fw	219.12±4.45 mg QE/ 100 g fw	[9]
	Leaf	Not recorded	Not recorded	68.32 mg RE/g dw	[10]
Morus alba	Fruits	5.68 to 40.46 mg GAE/g dw	0.51 to 28.61 mg/g dw	0.65 to 3.70 mg QE/g dw	[11]
	Leaf	51.43±1.11 mg GAE/g dw	Not recorded	43.75±0.78 mg QE/g dw	[12]
Morus rubra	Fruits	1035 mg GAE/ 100 g dw	Not recorded	219 QE/ 100 g dw	[6]
	Leaf	Not recorded	Not recorded	31.28±2.12 mg RE/g	[13]

GAE—gallic acid equivalent, C3GE—cyanidin-3-glucoside equivalent, RE—rutin equivalents, QE—quercetin equivalent, CE—catechin equivalents, fw—fresh weight, dw—dry weight

3.1 Mulberry fruits

M. nigra fruits contain anthocyanins, water-soluble colours. Many research revealed that anthocyanins are potent flavonoids and antioxidants, and that the structure, presence, and amount of copigments as well as the environment's acidity all affect the colour of anthocyanins. Anthocyanins are responsible for giving black mulberries their colour. Since anthocyanins are present, *M. nigra* L. generally has higher bioactive chemical levels than *M. alba* L. [14]. Nevertheless, anthocyanins were found in some species of white mulberries because they accumulate as fruit ripens, changing the fruit's colour from green (unripe) to white and light purple (at maturity). The amount of polyphenolic compounds and their functions in mulberry fruits have been recorded in a number of studies, and it varies greatly depending on the variety as well as the climate, soil, agronomic, and processing conditions. Cyanidin-3-O-glucoside is the primary pigment among the four main anthocyanins found in *M. nigra* [15]. There were found to be four pelargonidin and cyanidin anthocyanins in *M. nigra*, each conjugated with one, two, or three hexose sugars. Both white and black mulberries include the flavonol compounds quercetin and kampferol, which are esterified with one to three sugars or one to two sugars and one malonyl group (Table 2). Dihydroquercetin (taxifolin) hexoside and dihydrokaempferol hexoside, which are precursors of the biosynthesis of anthocyanidins like cyaniding and pelargonidin, respectively, were shown to be two flavanonols in black mulberries [16].

Table 2: List of the phenolic substances that have been identified from the mulberry tree's various parts

Species	Organs	Type of Sample	Technique	Identified Components in Morus sp.	References
M. nigra	fruits	Lyophilized samples	HPLC-DAD-ESI HRMS	Anthocyanins: cyanidin-hexoside, cyanidin-pentosyl-hexoside, cyanidin-rhamnosyl-hexoside, cyanidin-sambubiosyl-rhamnoside, cyanidin-sambubiosyl-glucoside; delphinidin-pentoside, delphinidin-dirhamnosyl-hexoside, petunidin-pentoside, peonidin-hexoside Proanthocyanidin (condensed tannins): procyanidin trimer 1 Flavonols: kaempferol-rhamnoside, kaempferol-hexoside, kaempferol-malonyl-hexoside, kaempferolrhamnosyl-hexoside, kaempferol-dihexoside; quercetin-rhamnoside, quercetin-hexoside, quercetin-malonyl-hexoside, quercetin-rhamnosyl-hexoside, quercetin-dirhamnosyl-hexoside, quercetin-rhamnosyl-dihexoside, rutin; myricetin-hexoside Flavone: apigenin-hexoside, apigenin-dihexoside Phenolic acid: chlorogenic acid	[17]
	leaves	Ethanolic extract	HPLC-DAD	Anthocyanins: cyanidin; Flavonols: quercetin; kaempferol. Flavonols: catechin. Phenolic acid: caffeic acid; coumaric acid.	[18]
	twigs	Powder	HPLC; LC-MS-MS; UV-spectra; IR-spectra	Prenylated flavonoids: morunigrols A, B, C, D; cudraflavone B; morusin; moracin C and P. Diels−Alder adducts: morunigrines A and B;	[8]
	roots bark	Air-dried roots bark	RP-MPLC; MS	Prenylated flavonoids: kuwanon L, G and H; cudraflavanonă A; morusin; chalcomoracin, norartocarpetin. Stilbenes: oxyresveratrol	-
Morus alba	fruits	Dry powder	UPLC-TUV/QDa	Flavonols: rutoside, morin, isoquercetin, quercetin, kaempferol	[19]
	leaves	Powder sample	HPLC-DAD	Flavonols: isoquercitrin; rutin; quercitrin, astragalin (kaempferol-3-O-glucoside). Coumarin: skimmin Phenolic acid: chlorogenic acid	[20]
	twigs	Powder sample	HPLC-DAD	Prenylated flavonoids: kuwanon G; morusin; Stilbenes: mulberroside A; oxyresveratrol Phenolic acid:4-hydroxycinnamic acid	[20]
	root bark	Powder bark samples	HPLC-DAD	Flavanonol: taxifolin Prenylated flavonoids: kuwanon G; morusin; Stilbenes: mulberroside A; oxyresveratrol Phenolic acid: chlorogenic acid;	[20]

3.2 Mulberry Leaves

The primary class of flavonoids found in mulberry leaves are flavonols, whose amounts vary by region. Neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, caffeoylquinic acid isomer, and caffeoylquinic acid glucoside were found in the leaves of *Morus* as caffeoylquinic acid derivatives [2]. Rutin and quercetin 3 (6-malonylglucoside), which are flavonol glycosides primarily responsible for the antioxidant capacity of the leaves and have properties that lessen oxidative stress in the liver and improve hyperglycemia, were also discovered to be the predominant flavonol glycosides in mulberry leaves. Mornigrol E, Mornigrol F, and morusin, a prenylated phenolic found in all parts of the mulberry plant with the highest concentration in the bark of the root, are other flavonoids that have been found in mulberry leaves.

3.3 Mulberry Twig and Root Bark

In Chinese herbal medicine, the root barks of mulberries, particularly *M. alba* L., were frequently used to cure a variety of illnesses. Prenylated flavonoids including morusin, kuwanon C (also called mulberrin), and kuwanon G are the primary components of root barks [21]. Diels-Alder-type adducts are another form of polyphenol that can be discovered in mulberries. The majority of these adducts contain flavonoid groups, while prenyls and their analogues can substitute for the flavonoid unit's C-2 and C-3. Kuk *et al*. (2017) examined the anti-disease Alzheimer's activity of the root bark of *M. alba* (Korea) by phytochemical analysis [22]. Oxyresveratrol, resveratrol p-coumaric acid, chrysin, catechin, vanillic acid, ferulic acid, chlorogenic acid, mulberroside A, maclurin, and moracins were discovered to be abundant in the phenolic phytochemicals in mulberry bark.

4. Health Benefits and Effects

The existence of polyphenolic chemicals from the genus *Morus* has recently drawn more interest and attention due to its biological effects, which include anticancer, anti-inflammatory, antidiabetic, antihypertensive, antinociceptive, antiaging, antianemic, antibacterial, and antioxidant activity. It is advised to use *M. nigra* fruits for the prevention and treatment of serious illnesses such diabetes, cancer, bacterial infections, arthrosclerosis, hyperlipidemia, neurological diseases, inflammation, and hypertension, as well as to enhance medications with their natural flavour and colour.

Presently, there is a lot of focus on immune stimulation as a means of disease prevention in people, and there is a growing amount of curiosity about the identification of natural compounds that have the capacity to boost immunity. The ability of plants to modify the immune system has drawn a lot of attention, especially in recent years as people have become more aware of this ability. The *M. nigra* plant's botanical sections include bioactive substances that have immunomodulatory effects on infectious illnesses with bacterial, parasite, and viral predisposing factors. As a result, the mulberry could be used to open up new possibilities for the creation of dietary supplements that have potent immunostimulatory and immunosuppressive effects and improve quality of life. Blood was made more watery by the mulberry root juice, which is also particularly effective against tapeworms and other intestinal parasites. Recently, it was shown that *M. alba* fruits can be utilised as an additive in dendritic-cell cancer immunotherapy because the polysaccharides in the composition cause dendritic cells to undergo phenotypic maturation [23]. Many studies have shown that different mulberry sections offer health-promoting qualities, including anti-inflammatory, neuroprotective, anti-atherosclerosis, hepato-and gastro-protective, antimicrobial, and anti-melanogenesis effects.

Another prevalent illness of neurodegeneration is Alzheimer's disease. By inhibiting the production of amyloid beta-peptide (1-42) fibrils, mulberry leaf extract offers a substantial source of treatment for Alzheimer's disease. The use of mulberry leaves decreased the risk of developing this illness.

As we now know, mulberry leaves contain chemical elements that lower high blood sugar levels (hyperglycemia) after a meal high in carbohydrates, which is why they have long been utilised in Chinese medicine for the prevention and treatment of diabetes. Current research on both humans and animals has found that mulberry or sericulture products containing DNJ reduce postprandial glucose rises. According to reports, several nitrogen-containing sugars found in mulberry leaf extract, particularly one known as 1-deoxynojirimycin, severely impede the intestinal metabolism of disaccharides (mainly sucrose), limiting the amount of monosaccharides that enter the bloodstream. Drinks made from mulberry leaf (*Morus alba*) are thought to be beneficial for everyone's health, but especially for diabetics.

5. Conclusion

The use of medicinal plants is still significant in rising and developing nations. One of the significant traditional herbs that has been utilised for decades in medicine is the mulberry plant. All of the mulberry tree's botanical components, including the fruits, leaves, twigs, and root bark, are high in nutrients and phytochemical substances and have a variety of therapeutic benefits. It contains a lot of flavonoids and other substances with potential antibacterial effects as well as free radical scavenging abilities. All components of the plant are utilised as medication because of its pharmacological qualities. Mulberry has been shown to protect the liver, enhance vision, make it easier for people to pass urine, lower blood pressure, fight diabetes, and control their weight. Mulberry leaves offer neuroprotective properties that can be utilised against neurological diseases like Parkinson's and Alzheimer's. They are also commonly used as food for silkworms and have high protein content. Researchers need to look into other beneficial benefits like immune-modulation and chemo-protective characteristics. Scientists desperately need to understand the therapeutic benefits of mulberries.

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