Phytochem Rev
https://doi.org/10.1007/s11101-025-10073-1

The multifaceted benefits of *Morus nigra* L.: a pharmacological powerhouse

Mustafa Özgür · Aslı Uçar · Serkan Yılmaz

Received: 5 September 2024 / Accepted: 2 January 2025
© The Author(s) 2025

Abstract The black mulberry (*Morus nigra* L.), a member of the Moraceae family, is a resilient plant known for thriving in diverse climates. It is valued for its rich composition of both primary and secondary metabolites, which contribute to a wide range of health benefits. Among the most significant of these are anthocyanins, which are responsible for the plant's antioxidant, anti-inflammatory, and antibacterial properties. Traditionally, *Morus nigra* has been widely used in Chinese and Indian medicine to treat a variety of conditions, including diabetes, hypertension, and neurodegenerative diseases. Recent scientific studies have supported these traditional uses, highlighting the plant's potential in modern medicine. Specifically, *Morus nigra* has demonstrated positive effects on cardiovascular health, blood sugar regulation, and tissue protection. The fruit of the mulberry is rich in primary metabolites such as carbohydrates, proteins, and essential fatty acids, enhancing its nutritional value. Secondary metabolites, including flavonoids and phenolic compounds, are particularly important for their role in reducing oxidative stress and inflammation. Additionally, *Morus nigra* has shown promising antidiabetic and antihyperlipidemic effects, influencing metabolic pathways related to insulin resistance and lipid regulation. Despite its many health benefits, caution is needed when using *Morus nigra* in supplement form, particularly in high doses. While the fruit is generally safe for consumption, studies on leaf extracts have revealed potential toxicity at elevated doses, emphasizing the need for careful dosage. Further research is essential to determine optimal intake levels and fully explore the plant's pharmacological potential.

Keywords Morus nigra · Phytochemistry · Pharmacology · Toxicology · Traditional use

Introduction

From seed to mature product, a variety of chemicals are generated to provide, protect, and preserve the vitality of plants. Primary metabolites include lipids, proteins, carbohydrates, and nucleic acids (Lazar 2003). Primary metabolites, which are present in high quantities, primarily influence the reproductive and nutritional processes of plant development (Alvarez 2014). The elements Carbon (C), Hydrogen (H), Oxygen (O), and Nitrogen (N), which together form

M. Özgür
Department of Nutrition and Dietetics, Faculty of Health Sciences, Mehmet Akif University, Burdur, Turkey

A. Uçar
Department of Nutrition and Dietetics, Faculty of Health Sciences, Ankara University, Ankara, Turkey

S. Yılmaz (✉)
Faculty of Nursing, Ankara University, Ankara, Turkey
e-mail: serkanyilmaz@ankara.edu.tr

Published online: 24 January 2025

the code of vitality through photosynthesis and nitrogen cycle processes, combine to form primary metabolites, which are primarily synthesized from Krebs cycle intermediates in the energy production mechanism (Mann 2021). Metabolites synthesized using substrates or end products resulting from the metabolism of primary metabolites are called secondary metabolites. Secondary metabolites are compounds found in low concentrations that are not directly related to the basic vital activities of the plant but are at least as important as primary metabolites (Twaij and Hasan 2022). Secondary metabolites are evaluated under 4 main groups as phenolic compounds produced by shikimate or malonate, terpenoids synthesized from isopentenyl diphosphate, nitrogen or sulfur/sulfur containing and minor structure metabolites. The main function of secondary metabolites in plants is to maintain the highly complex mechanisms developed for defense, protection, adaptation to the environment, survival and continuation of their generations (Saxena et al. 2013). In addition to these functions, they provide the tissues with their unique color, such as anthocyanins, carotenoids and betalains (Malabadi et al. 2022). In addition, secondary metabolites are used in industrial areas such as paint, fiber, glue, oil, flavor, perfume and medicine (Chiocchio et al. 2021). Different plant species have varying amounts of secondary metabolites, which vary based on both internal and external variables such soil type, climate, and genetic variants. Safe intake levels, various health benefits, and toxicological consequences have been the subject of increased research in recent years due to the growing interest in the pharmacological and toxicological effects of secondary metabolites. A review of the research is included along with information on the chemical composition of black mulberry (*Morus nigra*), a member of the mulberry family that has therapeutic effects on endocrine systems due to its secondary metabolites, as well as the health benefits of these metabolites, the use of nutraceuticals, and safe intake levels.

Because of its exceptional adaptability to various temperature and soil circumstances, the mulberry (*Morus* spp.), which is a fruit species that belongs to the *Morus* genus of the *Moraceae* family of the *Urticales* order, can thrive in temperate, tropical, and subtropical climate zones, topography, and soil conditions (Ercisli and Orhan 2007; Yilmaz et al. 2012). Originating from temperate regions of Asia, mulberry

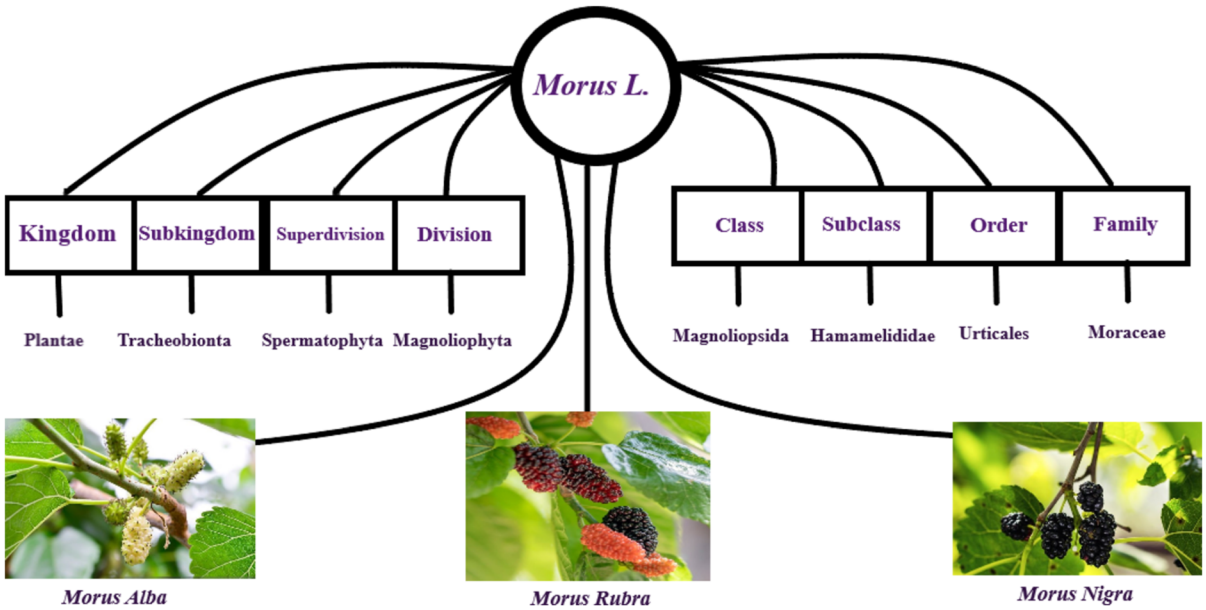


Fig. 1 Scientific classification of *Morus* L. (Jan et al. 2021)

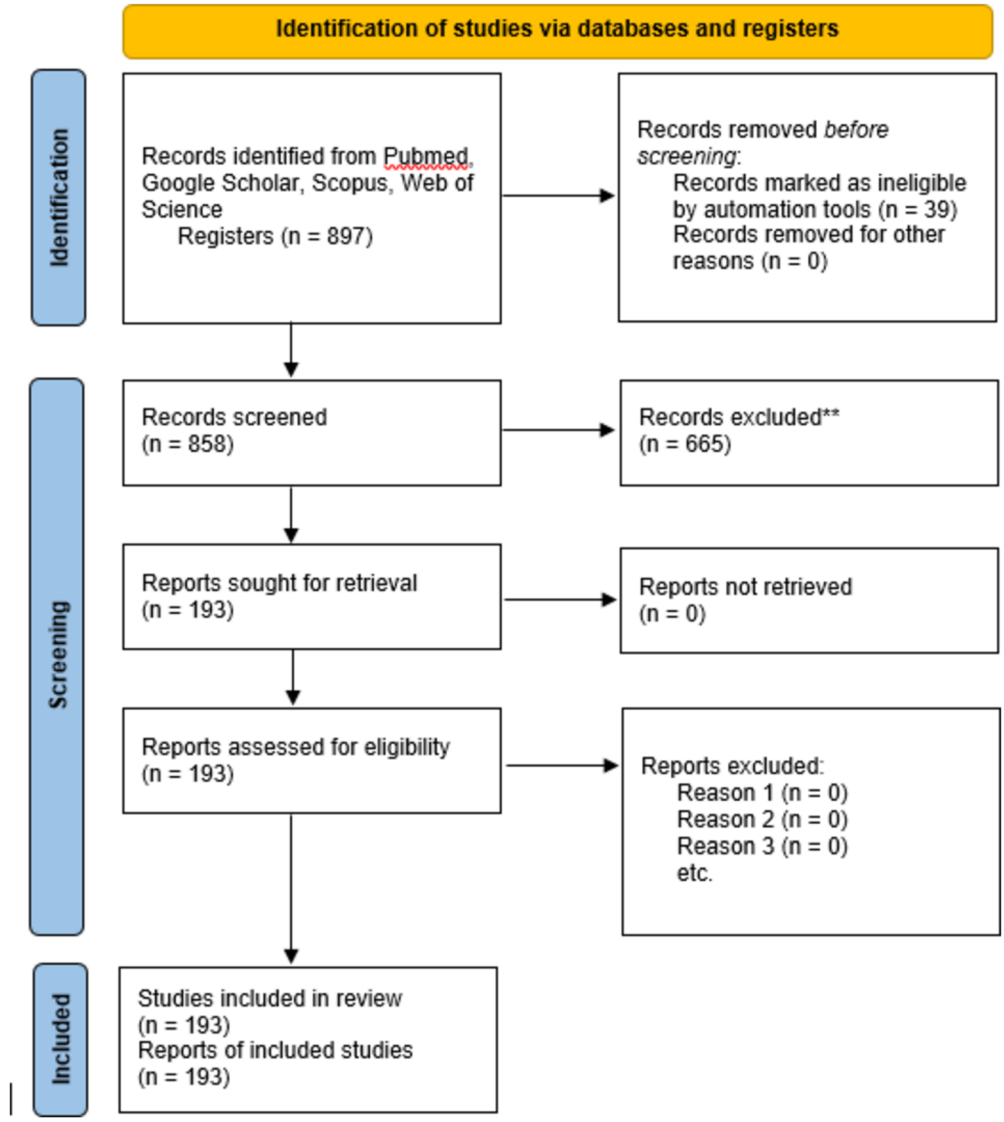


Fig. 2 PRISMA flowchart

is a perennial plant with a high structure that is widely dispersed. This plant can thrive in a wide range of climates, from the tropics to the sub-arctic and up to 4000 m above sea level. It normally prefers calcareous-clayey and southern soils, and it is not greatly impacted by drought (Vijayan et al. 2011). 10–12 of the roughly 100 species of the *Morus* genus, 68 species and one subspecies, that have been described are regularly farmed in the world's mild climate zones (Rodrigues et al. 2019). Recently, variations having both male and female flowers can be found alongside pistillate, staminate, and even hermaphrodite species (Memete et al. 2022). Among these, *Morus nigra* L. (black mulberry), *Morus rubra* L. (red mulberry), and *Morus alba* L. (white mulberry) are the three main species and grow all over the world (Fig. 1) (Brandão et al. 2021; Jan et al. 2021). Although they are named by their colors, it is not possible to understand the type

Table 1 Nutritional composition of *Morus nigra*

Chemical composition	References							
	Ercisli and Orhan (2007)	Imran et al. (2010)	Paunović et al. (2020)	Islamova (2022)	Babazadeh Darjazi and Jaimand (2023)	Sakar et al. (2023)	Saeed et al. (2023)	Othman et al. (2024)
Carbohydrates (%)	–	13.83	–	–	8.98–13.2	–	–	8.18
Glucose (g/100 g)	–	–	7.9–8.5	8.07	4.85–7.11	6.98–8.03	–	–
Fructose (g/100 g)	–	–	11.5–12.5	4.91	4.1–6.15	6.72–7.76	–	–
Protein (%)	8.9–10.9	0.96	1.37–1.45	–	–	–	–	–
Lipid (%)	0.95	0.55	–	–	–	–	–	–
Linoleic acid (%)	61.9	–	–	–	–	–	–	–
Palmitic acid (%)	12.1	–	–	–	–	–	–	–
Oleic acid (%)	14.8	–	–	–	–	–	–	–
Vitamins								
Tiamine	–	–	0.095	0.04	–	–	–	–
Riboflavin (mg/100 g FW)	–	0.04	0.097	0.03	–	–	–	0.086
Niacin (mg/100 g FW)	–	1.60	3.94	0.1	–	–	–	2.93
Ascorbic acid (mg/100 mL)	21.8	15.37	19.78	29.0	–	20.4–27.6	–	–
Minerals								
Ca (mg/100 g)	132	470	27.04	28.7	–	–	18.5 ± 0.3	126.67
P (mg/100 g)	232		231.05	–	–	–	103.48 ± 0.03	276.0
Mg (mg/100 g)	106	240	23.4	54.6	–	–	27.7 ± 0.2	–
Na (mg/100 g)	59	272	25.5	14.0	–	–	74.2 ± 0.2	53.67
K (mg/100 g)	922	1270	207.7	309.8	–	–	231.9 ± 0.2	1412.67
Fe (mg/100 g)	4.2	77.6	1.4	2.4	–	–	1.7 ± 0.0	4.58
Cu (mg/100 g)	0.4		0.58	0.03	–	–	0.81 ± 0.04	–
Zn (mg/100 g)	3.2	59.20	0.3	0.38	–	–	0.5 ± 0.07	6.18
Mn (mg/100 g)	4.2	–	–	0.03	–	–	–	2.47
Ni (mg/100 g)	–	1.60	–	0.02	–	–	–	2.09

of mulberry from the color of the fruit. For example, *Morus alba* fruit can be white, purple or black. *Morus rubra* is dark red–black. *Morus nigra* is dark purple, almost black, and is the most preferred among mulberries because it is generally large, juicy and has a balanced sugar-acid ratio (Ercisli and Orhan 2007). The first reports of *Morus alba* were from China, Europe, and North America. Because *Morus nigra* is native to Iran and the Caucasus, it is also known as Persian black mulberry. North America is the native home of *Morus rubra* (Barbour et al. 2008)). The largest mulberry growing countries are India and China and there are potential gene reserves for mulberry conservation in Uttarakhand, Nandadevi,

Table 2 Secondary metabolites of *Morus nigra*

Secondary metabolites	References								
	Pawlowska et al. (2008)	Gundogdu et al. (2011)	Thabti et al. (2011)	Aljane and Sdiri (2016)	Chen et al. (2017)	Wang et al. (2022a, b, c)	Skrovankova et al. (2022)	Sakar et al. (2023)	Khadivi et al. (2024)
Total phenolics (mg GAE/100 g)	–	–	598.6	30.45	–	11.91–26.10[a]	–	1.656–2.348	232.3–1777.7
Total flavonoids (mg GAE/100 g)	–	–	440.5	19.86	–	1.54–2.86[b]	–	–	32.2–306.2
Total anthocyanins (mg/g dry wt)	–	–	7.26	10.05	–	2.91–11.86	–	6.2–8.0	5.8–47.56
Cyanidin-3-O-glucoside (mg/g)	1.79	–	–	–	8.22	–	–	–	–
Cyanidin-3-O-rutinoside (mg/g)	0.75	–	–	–	2.86	10.01–92.06[c]	–	–	–
Pelargonidin-3-O-glucoside (mg/g)	0.12	–	–	–	0.25	0.12–0.68[c]	–	–	–
Quercetin-3-O-rutinlside (mg/g)	–	–	–	–	0.45	–	–	–	–
Isoquercetin (mg/g)	–	–	–	–	0.16	–	–	–	–
Quercetin (mg/g)	–	0.113	–	–	0.07	5.41–35.14[c]	0.04–0.09	–	–
Chlorogenic acid (mg/g/fw)	–	3.106	–	–	–	5.6–20.0[c]	5.9–9.1	–	–

a: mg GAE/g DW; b: mg RE/g DW; c: mg/kg DW

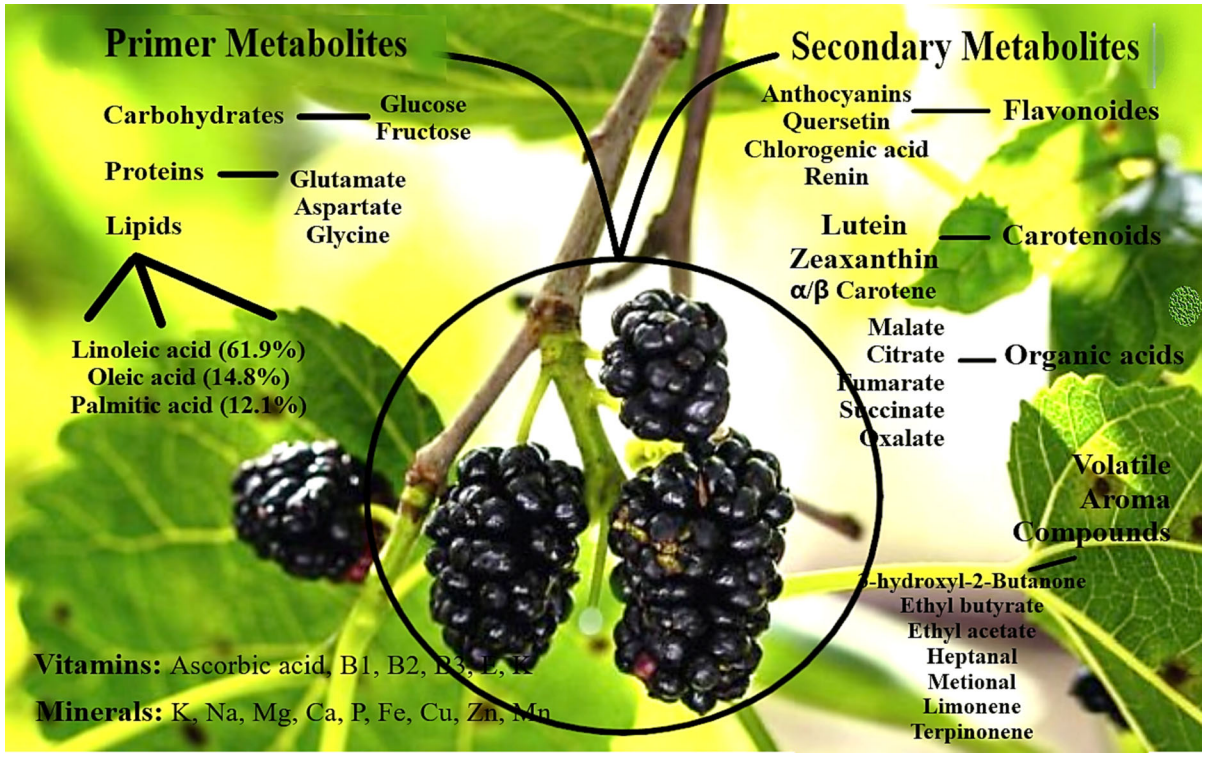


Fig. 3 Chemical composition of *Morus nigra* L

Namdapha, Kaziranga, Manas, Nokrek, Andaman and Nicobar Islands National Parks in India (Ananda et al. 2003). In these countries, mulberry is grown for its leaves, which are the most important food source for silkworms (*Bombyx mori* L.) (Ercisli and Orhan 2007). Despite this, in European countries such as Türkiye and Greece, mulberry is grown for its fruit rather than its leaves (Buğrut et al. 2023; Can et al. 2021; Wang et al. 2023).

Mulberry root, leaf, stem and fruit can be used in different areas (Kirac et al. 2024; Radojkovic et al. 2014). With the growth of the functional food industry, mulberry leaves, which were formerly used to feed silkworms, are now frequently employed for pharmacological purposes and have a substantial economic impact in Türkiye (Gundogdu et al. 2017). In addition, it is known that mulberry trees are used in the paper industry, furniture, and the production of some musical instruments (Łochyńska and Oleszak 2013; Rahman and Islam 2021). Some mulberry species are used as hedge plants in addition to being significant attractive plants in landscape design (Abdelnaby et al. 2021; Blitek et al. 2022). Fresh or dried mulberry fruit is consumed, and mulberries are also used to make tea, jam, molasses, marmalade, ice cream, noodles, and other foods (Askin et al. 2022; Ghanem et al. 2022; Vijayan et al. 2014; R. Zhang et al. 2022). Historically, mulberry fruits, roots and bark have been used in functional medicine to treat sore throat, anemia, iron deficiency anemia, hypertension, diabetes and arthritis; as an antipyretic, antibiotic and diuretic to protect the liver, treat vision problems, reduce blood pressure and prevent cardiovascular diseases (Dadhwal and Banerjee 2023). Especially in traditional Chinese medicine, *Morus nigra* is used in different ways in the treatment of dizziness, tinnitus, blurred vision, coronary heart disease, anemia, cancer, dysentery, hypertension, diabetes, diarrhea, constipation, asthma, Parkinson's etc., in the removal of intestinal worms, as an expectorant and antipyretic (Luo et al. 2019; Yadav et al. 2022).

The *Morus* genus within the *Moraceae* family contains more than 100 subspecies. The most widely

Table 3 Organic acids of *Morus nigra*

Organic acids	References							
	Gundogdu et al. (2011)	Eyduran et al. (2015)	Bozhüyük et al. (2016)	Can et al. (2021)	Islamova (2022)	Skrovankova et al. (2022)	Sakar et al. (2023)	Mahmood et al. (2024)
Malic acid (g/100 g/fw)	1.323	1.210–3.040	5.215	2.233–7.452	1.216	6.02–11.44	6.33–10.45	6.33
Citric acid (g/100 g/fw)	1.084	0.733–1.033	8.855	0.717–2.134	2.190	2.41–4.02	2.55–4.10	2.38
Tartaric acid (g/100 g/fw)	0.123	0.147–0.297	0.115	0.126–0.199	–	0.37–1.05	0.48–1.04	0.69
Succinic acid (g/100 g/fw)	0.342	0.117–0.360	0.755	0.067–1.127	–	–	–	–
Lactic acid (g/100 g/fw)	0.049	–	0.329	–	–	–	–	–
Fumaric acid (g/100 g/fw)	0.011	0.010–0.107	0.015	0.032–0.172	–	–	–	–
Acetic acid (g/100 g/fw)	0.019	–	0.054	–	–	–	–	–
Oxalic acid (g/100 g/fw)	–	–	–	–	–	0.54–1.18	2.90–4.11	0.99

Table 4 Antioxidant activity of *Morus nigra*

	Experimental method					References
	DPPH	ABTS	FRAP	CUPRAC	β-CB	
Concentrations	–	0.51–1.44 mg TE/100 g	9.9–16.9 µmol TE/g fw	–	–	Özgen et al. (2009)
	0.0362–0.1291 mg TE/100 g	0.0384–0.2073 mg TE/100 g	–	–	–	Sánchez-Salcedo et al. (2015)
	946 mg TE/100 g	2788 mg TE/100 g	1836 mg TE/100 g	4046 mg TE/100 g		Tomas et al. (2015)
	–	69.10 ± 1.88 µg/mL	–	–	41.30 ± 12.80%	Souza et al. (2017)
	549.1–1386.1 GAE µg/mg	172.6–2521.5 TE µg/mg	–	124.64–124719.3 TE µg/mg	–	Abay and Eruygur (2021)
	28.48–100.11 mg AAE/g DW	13.49–73.06 mg AAE/g DW	10.05–48.35 mg AAE/g DW	–	–	Wang et al. (2022a, b, c)
	–	8.62 ± 0.72 µg/mL	0.989 µmol TE/g fw	–	–	Vukmirović et al. (2023)
	87.45 mmol TE/100 g	215.06 mmol TE/100 g	303.87 ± 5.95 µmol TE/g fw	–	–	Serio et al. (2024)
	13.92 ± 1.62 mg/mL	–	169.00 ± 4.58 µmol TE/g fw	–	–	Kolaylı et al. (2024)
	227.09–1150.47 mg AAE/100 g	–	–	–	–	Khadivi et al. (2024)
	56.30 ± 0.96 AAE µg/mL	–	–	–	–	Martins et al. (2024)
	1.01–5.57 µmol TE/g fw	–	2.21–20.85 µmol TE/g fw	–	–	Uyak et al. (2024)

DPPH, 1,1-difenil-2-pikril hidrazil; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline)-6-sulfonic acid; FRAP, Fe^{+2} reducing antioxidant power; CUPRAC, CU^{+2} reducing antioxidant capacity; β-CB, β Carotene Blanching

Table 5 Antibacterial and antifungal activity of *Morus nigra*

Microorganism	References
Escherichia coli	Kumar et al. (2015)
Staphylococcus aureus	
Pseudomonas aeruginosa	
Klebsiella pneumoniae	
Salmonella typhimurium	
Bacillus subtilis	Ahmad and Ahmed (2016)
Escherichia coli	
Pseudomonas aeruginosa	
Escherichia coli	Bahi et al. (2016)
Staphylococcus aureus	
Klebsiella pneumonia	
Bacillus cereus	
Candida albicans	
Acinetobacter sp.	
Aspergillus niger	
Fusarium oxysporum	
Aspergillus fumigates	
Aspergillus flavus	
Staphylococcus epidermidis	Aulifa et al. (2017)
Propionibacterium Acnes	
Bacillus cereus	Souza et al. (2017)
Enterococcus faecalis	
Escherichia coli	
Klebsiella pneumoniae	
Salmonella choleraesuis	
Serratia marcescens	
Shigella flexneri	
Staphylococcus aureus	
Staphylococcus aureus	Miljković et al. (2018)
Staphylococcus epidermidis	
Streptococcus pyogenes	
Enterococcus faecalis	
Propionibacterium acnes	
Escherichia coli	
Pseudomonas aeruginosa	
Acinetobacter baumannii	
Proteus mirabilis	
Klebsiella pneumoniae	
Bacillus subtilis	Zhou et al. (2019)
Staphylococcus aureus	
Escherichia coli	
Proteus vulgaris	
Candida albicans	
Candida glaborata	
Streptococcus mutans	Budiman and Aulifa (2020)
Streptococcus mutans	Aulifa et al. (2021)
Enterococcus faecalis	Trak and Arslan (2021)
Listeria monocytogenes	
Bacillus cereus	
Staphylococcus aureus	
Salmonella Typhimurium	
Enterobacter aerogenes	
Klebsiella pneumoniae	
Escherichia coli 0157:H7	
Salmonella enterica	
Staphylococcus aureus	Melo et al. (2022)
Escherichia coli	
Pseudomonas aeruginosa	
Klebsiella pneumoniae	
Shigella flexneri	
Serratia marcescens	
Staphylococcus aureus MRSA	
Salmonella choleraesuis	
Staphylococcus epidermidis	Sharifee et al. (2022)
Staphylococcus aureus	
Streptococcus mutans	
Streptococcus pyogenes	
Pseudomonas aeruginosa	
Candida albicans	Dheeb and Al-Samarraie (2023)
Candida tropicalis	
Candida kruzei	
Candida parasilosis	
Cryptococcus neoformans	
Trichophyton rubrum	
Aspergillus fumigatus	

used species in the food, pharmaceutical, and silkworm industries are *Morus nigra*, *Morus alba*, and *Morus rubra*; other frequently used species include *Morus latifolia*, *Morus cathayana*, *Morus atropupurea*, *Morus bombycis*, *Morus wittiorum*, and *Morus multicaulis* (Vijayan et al. 2011; Zhao et al. 2005). Mulberry species *Morus alba*, *Morus nigra*, and *Morus rubra*, whose fruits are used and widely cultivated, have come to the fore because they have more bioactive components and therapeutic potential than other mulberry species (Can et al. 2021). It is

stated that 95% of the mulberry tree potential in Türkiye belongs to *Morus alba*, 3% to *Morus rubra* and 2% to *Morus nigra* (Ercisli 2004). It is estimated that the reason for the lower rates of the *Morus nigra* species is that the products are offered for direct sale in local markets or have lower yields (Cüce 2024).

Material and methods

The aim of the present study was to conduct a review of the pharmacological and toxicological profile of the *Morus nigra*. The study was based on a systematic approach.

Criteria for inclusion and exclusion

The systematic review included all pharmacological and toxicological profile of the *Morus nigra* and was not limited to a specific period of time. Both research and review articles were included in the present study. However, studies in languages other than English were excluded.

Procedure

Two researchers searched the databases independently in 2024. As the subject of the study comprises a medical nature, the search of the relevant literature was primarily concentrated on the Scopus, Google Scholar, PubMed and Web of Science databases. The search procedure included a combination of the terms *Morus nigra*, black mulberry, pharmacology, toxicology, phytochemistry. In the search, a total of 858 studies were reviewed. As a result, 193 of the reviewed articles were classified as appropriate and included in the study, as shown in the PRISMA flowchart (Fig. 2).

Chemical composition of *Morus nigra*

Morus nigra, whose homeland is Iran, is a tree with 28–308 chromosomes, typically monoecious, can grow up to 10–13 m tall, grows in warm and humid climate regions and sheds its leaves in winter (Kruthika et al. 2023). Its fruit is dark purple, almost black; It is an edible fruit with a fruiting period of 8–10 weeks, consisting of several small seed clusters that are 2–3 cm long when ripe. *Morus nigra*, which is quite delicious with its balanced sugar-acid ratio; it is similar to *Morus rubra* in taste and is known to be more delicious than *Morus alba* (Gundogdu et al. 2017).

Because primary and secondary metabolites in plants are influenced by several geographical elements, including soil, climate, altitude, temperature, harvest time, and post-harvest storage conditions, they differ in their chemical composition (Gundogdu et al. 2018). The primary metabolites that provide sweetness in fruits are saccharides, most commonly fructose/glucose, and generally occur during the ripening process of the fruit (Muir et al. 2007; Okatan et al. 2022). The overall carbohydrate content of *Morus nigra* fruits is 5–10 g/100 g of fruit weight. Glutamate is the most common amino acid in *Morus* species, making up about 20% of the total. Glycine and aspartate are the next most abundant amino acids. Additionally, *Morus nigra* has larger levels of histidine, proline, and lysine than *Morus alba* (Hao et al. 2022). Despite its low protein and lipid levels, it's also contains essential fatty acids that the human body cannot synthesize (essential) for the formation of healthy cell membranes, proper functioning of the brain and nervous system, and the production of eicosanoids (Ali Redha et al. 2023). *Morus nigra*, which is also rich in micronutrients, contains vitamins, mostly ascorbic acid (Vitamin C), and minerals, mostly potassium (K) (Table 1). Although toxic heavy metal levels are low, harmful effects of fruits consumed through irrigation water or soil contamination can also be seen (Ercisli and Orhan 2007; Radojkovic et al. 2014).

Secondary metabolites of *Morus nigra*

Plants produce secondary metabolites to defend themselves against threats, but they are not necessary for them to live. These substances include sulfur compounds, alkaloids, phenolic compounds, and terpenoids. Consuming fruits and vegetables high in phenolic compounds lower the risk of heart disease, cancer, neurological disorders, and chronic diseases (Boranbayeva et al. 2014). Secondary metabolites with anti-oxidant, anti-mutagenic, and anti-carcinogenic qualities, such as flavonoids, alkaloids, gamma amino butyric acid (GABA), and carotenoids, are also abundant in *Morus nigra* fruit (Can et al. 2021; Ercisli

and Orhan 2007). Of these metabolites, flavonoids, such as routine and chlorogenic acid, have the largest concentrations. Fruits that are blue-purple in color are also attributed to flavonoids called anthocyanins, which are present in high concentrations in *Morus nigra* fruits (Özgen et al. 2009). It does not exhibit any dominating color characteristics while containing carotenoids such as lutein, zeaxanthin, and α/β-carotenes (Thabti et al. 2011). *Morus nigra* is rich in non-anthocyanins such as quercetin-3-rutinoside, kaempferol-3-rutinoside, and quercetin-3-glucoside, and anthocyanins such as cyanidin-3-glucoside, cyanidin-3-rutinoside, cyanidin-3-sophoroside, pelargonidin-3-glucoside, and pelargonidin-3-rutinoside (Table 2.) (Huo et al. 2023). In plant metabolism, organic acids function as osmotic anions and intermediate products during the conversion of various chemicals. In plants, organic acids including malate, citrate, fumarate, α-ketoglutarate, and oxalo-succinate are part of the Krebs cycle and generate the C skeleton that is needed to convert amino acids into protein molecules (Panchal et al. 2021). It is also rich in organic acids such as malic acid, citric acid, fumaric acid, tartaric acid and succinic acid, which help improve taste (Table 3.) (Can et al. 2021; Eyduran et al. 2015). Furthermore, 40 different volatile aroma compounds are identified in *Morus nigra*, including ethyl acetate, heptanal, methional, hexanal, trans-2-hexanal, 2-octenone, limonene, terpinonen, decanoic acid, ethyl decanoate, acetic acid, and 3-hydroxyl-2-butanone (Calín-Sánchez et al. 2013) (Fig. 3).

Pharmaceutical effects of *Morus nigra*

Since ancient times, traditional medicine has employed plants to cure many illnesses. It is well known that certain chemicals included in fruits and vegetables may assist treat specific diseases (Halberstein 2005). *Morus nigra* has also been used in traditional medicine for many years, especially in China and India. (Feng et al. 2015; Manzoor and Qayoom 2023). In recent years, a great deal of research has been done on the various secondary metabolites that are present in the leaves, seeds, branches, and fruits of *Morus* species. These metabolites have been shown to have antioxidant, antinociceptive, antibacterial, anti-melanogenic, anti-inflammatory, antidiabetic, and antihyperlipidemic effects, as well as organ protective properties that reduce damage at the cellular and tissue level (Aulifa et al. 2017; Chen et al. 2016, 2017; Wang et al. 2022a, b, c). At the same time, it has been shown that it is effective in the treatment of neurological diseases such as Parkinson and Alzheimer (Güçer Öz et al. 2024; Siddique et al. 2023; Talo Yildirim et al. 2019). There are hundreds of different secondary metabolites identified in *Morus nigra* species and all of them are used in both traditional and modern medicine in the treatment of diseases indicated by different mechanisms.

Antioxidant activity

Oxidizing chemicals, which include reactive oxygen, nitrogen, sulfur, and carbonyl derivatives, are produced by metabolic processes within cells and stressors in the environment (Sies et al. 2017). These compounds change the pH concentrations on the cell, disrupt the cell membrane integrity, degenerate the cell and cause vital activities to stop (Shinde et al. 2012). Another way to describe oxidative stress is as the state that results from the body's antioxidant defense system being over extended. Ageing, cancer, diabetes, atherosclerosis, chronic inflammation, neurological diseases, and ischemia reperfusion disorders are all significantly impacted by oxidative stress (Sies et al. 2017). Substances that prevent oxidation caused by free radicals and have the ability to capture and stabilize free radicals are called antioxidants. Antioxidants are molecules responsible for limiting radical formation, terminating radical reactions, neutralizing formed radicals and eliminating damaged molecules, and they minimize possible damage to the body by binding free radicals to themselves or neutralizing them (Gulcin 2020).

Antioxidants are examined in two groups as natural and artificial antioxidants. Superoxide dismutase (SOD), catalase, peroxidase, glutathione reductase, glutathione-S-transferase are known as enzymatic natural antioxidants. Minerals such as copper, zinc, selenium, which are cofactors of these enzymes, are also expressed as antioxidant effective minerals. Components found in the blood such as glutathione, ceruloplasmin, bilirubin, albumin, and ferritin are endogenous antioxidants. In addition, vitamins A, C, and E found in vegetables and fruits are important exogenous antioxidant sources. Ethoxyquin, butylated

hydroxy anisole, butylated hydroxy toluene, propyl gallate, and tertiary butyl hydroquinone, which have been synthesized synthetically since the mid-twentieth century, are artificial antioxidants that have survived to the present day due to their preservative purposes in foods and their prevention of fat oxidation (Flieger et al. 2021; Girish et al. 2023). However, there are studies showing that the use of high amounts of artificial antioxidants causes toxicity on the cell (Esazadeh et al. 2024; Xu et al. 2021).

Certain secondary metabolites included in fruits and vegetables are known to have potent antioxidant properties. Fruits with a high anthocyanin content in particular have a strong antioxidant activity. Blue-purple fruits including blackberries, strawberries, raspberries, cranberries, elderberries, and black mulberries are a few examples of these fruits (Bezerra et al. 2024). The species of *Morus* L. with the highest anthocyanin content is *Morus nigra*. Tables 1 and 2 demonstrate the abundance of vitamins C and E, carotenoids, phenolic compounds, and antioxidant-producing chemicals called anthocyanins found in *Morus nigra*. Furthermore, it is regarded as a significant source of antioxidants because to its copper and zinc content.

Proximetric and colorimetric techniques can be used to identify antioxidant chemicals in food in vitro. The antioxidant capacity of *Morus nigra* was assessed using a variety of methods in the fruit, including hydroxyl radical (OH–) scavenging, trolox equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP), copper (II) reducing antioxidant capacity (CUPRAC), oxygen radical absorption capacity (ORAC), folin-ciocalteu (FC), 2,2′-azino-bis (3-ethylbenzothiazoline)-6-sulfonic acid (ABTS), and lipid peroxidation (Lim and Choi 2019). Table 4 summarizes the results of some recent studies.

Anti-inflammatory effect

When physical, chemical, or infectious agents cause damage, harm, or destruction to tissues, the body responds by producing inflammation. Tissue damage or injury is caused by stimulatory, inhibitory, suppressive, or blocking reactions that are coordinated by intricate cellular connections between cells (Meizlish et al. 2021). These responses are mediated by low molecular weight cytokines, chemokines, and eicosanoids released from immune cells. While some of these mediators cause anti-inflammatory reactions, others cause pro-inflammatory ones. TNF-α, interleukin (IL) 1 family, IL-6, and interferons are the most significant and researched proinflammatory cytokines, and they have a role in the development of numerous chronic diseases (Mohammed Bakheet et al. 2024; Zhang and Dhalla 2024; Zhang et al. 2024). Some studies have shown that some compounds obtained from *Morus nigra* leaves and seeds inhibit edema development and granulation, which are stages of inflammation. (Padilha et al. 2010; Wang et al. 2010). It is well recognized that anthocyanins, particularly those in food, have this function. Research has demonstrated that cyanidin-3-O-glucoside inhibits the formation of prostaglandin E2 (PGE2), IL-8, nitrite oxide (NO), and cyclooxygenase-2 (COX-2) as well as the expression of iNOS and iNOS-related proteins, hence reducing cytokine-induced inflammation in intestinal cells (Khoo et al. 2017; Liu et al. 2021; Serra et al. 2013).

Wang et al. (2010) reported that Mornigrol D and norartocarpetin obtained from *Morus nigra* roots inhibited the release of β-glucuronidase from polymorphonuclear leukocytes in rats. Chen et al. (2016) reported that proinflammatory cytokines such IL-1β, TNF-α, and IFN-γ were reduced by cyanidin-3-O-glucoside (8.3 mg/g) and cyanidin-3-O-rutinoside (2.9 mg/g). In another study, rats with sepsis in *Morus nigra* showed a large increase in the anti-inflammatory cytokine IL-10 and a significant drop in the levels of hepatic IL-1β and IL-6 (de Pádua Lúcio et al. 2018). *Morus nigra* was found to have an anti-inflammatory impact because of its anthocyanin concentration in another study assessing the plant's ability to heal wounds and reduce inflammation (Zhou et al. 2019). The anti-inflammatory properties of *Morus nigra* leaves on human red blood cells were demonstrated by Thakur et al. (2020). According to Elmasry and Moawad (2021), *Morus nigra* was found to have a considerable protective effect against liver damage generated by carbon tetrachloride by lowering the levels of pro-inflammatory cytokines such as TNF-α and interferon-γ. Another study reported that *Morus nigra* leaves suppressed inflammation by activating peroxisome proliferator-activating receptor (PPAR) in lipopolysaccharide-induced murine macrophage cells (Carneiro et al. 2022). In contrast to these studies, Padilha et al. (2010) claimed that the compounds such as betulinic acid, β-sitosterol, and germanicol present

in *Morus nigra* leaves are responsible for the anti-inflammatory activity. Chronic degenerative diseases like cancer, diabetes, and cardiovascular disease can be effectively prevented by inhibiting pro-inflammatory cytokines. Consequently, a list of *Morus nigra*'s effects on these illnesses is also provided below.

Antidiabetic effect

Diabetes mellitus (DM) is a metabolic disorder marked by dysregulation of blood glucose levels. It is a pathological condition associated to the generation of insulin from the pancreatic beta cells, its release via exocytosis, and its usage by attaching to its receptor in numerous cells (American Diabetes Association (ADA), 2020). Insulin resistance, also known as the inability of insulin to connect to its receptor, is another factor contributing to its symptoms, although it can also arise from insufficient or absent insulin output as a result of beta cell injury (Lawrence 2021). These two disorders have a variety of causes, but oxidative damage and increased release of proinflammatory cytokines are most likely to be involved (Amirshahrokhi and Zohouri 2021). Oxidative stress and proinflammatory cytokine levels rise concurrently with noncompliance with clinical diet and medication therapy in individuals with diabetes. Nowadays, the rise in obesity brought on by altered eating patterns and environmental factors also raises the prevalence of DM (Ruze et al. 2023). In the presence of obesity, high secretion of adipokines such as resistin, chemerin, visfatin, and TNF-α and IL-6 from adipose tissue and low levels of adipokines such as adiponectin and omentin have been associated with DM (Kwon and Pessin 2013). Because of their antioxidant and anti-inflammatory properties, secondary metabolites discovered in the seeds, branches, leaves, and fruits of *Morus nigra* may provide protection against the onset of obesity and diabetes mellitus.

The effects of *Morus nigra* on blood glucose regulation have been studied for years. In the past ten years, research has concentrated on extracts made using various methods from *Morus nigra* leaves. A study found that an extract of *Morus nigra* leaves at a dose of 500 mg/kg improved DM by inhibiting oxidative stress (Araujo et al. 2015). Y. Liu and Yang (2015) investigated the effects of several leaf portions of *Morus nigra* on mice given a high-fat, high-glucose diet caused by streptozotocin. It was observed that the aqueous extract groups of *Morus nigra* had suppressive actions on the insulin resistance index, lipids, and fasting blood sugar of mice with type 2 DM. 200 mg/kg and 400 mg/kg *Morus nigra* leaf extract were found to improve pro-oxidant status and hyperglycemia in similar study (Júnior et al. 2017). Serum insulin levels were found to be significantly higher in the total phenolic and total flavonoid extracts from *Morus nigra* leaves administered to male albino rats by Hago et al. (2021) at two different doses (250 mg/kg and 500 mg/kg) for four weeks. Hexane fractions of *Morus nigra* leaves (400 mg/kg) have been shown to be useful in avoiding postprandial hyperglycemia and fasting blood glucose levels for 21 days (Silva et al. 2021). Tang et al. (2022) administered streptozotocin-induced diabetic rats 100 mg/kg and 200 mg/kg of extracted *Morus nigra* branches for a period of four weeks. By inducing the release of p-AMPK, p-PKC, and GLUT-4, both dosages were found to have antihyperglycemic effects at the conclusion of the study. Even so, 1-Deoxynojirimycin was the primary factor in blood sugar management in a trial on diabetic patients where the antidiabetic benefits of *Morus nigra* were documented (Momeni et al. 2022). Similarly, nigranol A and B isolated from *Morus nigra* branches, as well as sanggenone, nigrasin C and A have been reported to have a blood sugar lowering effect by inhibiting the α-glucosidase enzyme (Xu et al. 2020). Nigragenon isolated from *Morus nigra* branches also has insulin sensitizing effects (Wang et al. 2022a, b, c). Additionally, Ren et al. (2022) shown that by lowering levels of proinflammatory cytokines TNF-α and IL-6, *Morus nigra* enhances insulin sensitivity.

It is obvious that the secondary metabolites that are isolated from the branches, leaves, and fruits of *Morus nigra* are primarily responsible for the plant's antidiabetic properties. Despite the fact that diabetes mellitus mostly results from insufficient or insufficient insulin secretion, research have demonstrated that *Morus nigra* has antidiabetic benefits through a variety of metabolic pathways because of the many processes involved in the disease's pathogenesis. Because fruit contains fructose and glucose, it is not a very effective means of regulating blood sugar. Furthermore, the levels at which antidiabetic benefits are demonstrated are higher than the daily allowance for fruit consumption. Furthermore, a study has demonstrated that leaf extracts from *Morus nigra* can raise blood sugar levels (Hemati et al. 2010).

Antihyperlipidemic effect and cardiovascular diseases

The most significant risk factor for cardiovascular diseases, which rank among the world's top chronic disease-related causes of mortality, is hyperlipidemia (Nelson 2013). Atherosclerosis is the initial phase in the process that leads to cardiovascular diseases. Endothelial dysfunction is brought on by low-density lipoprotein (LDL) oxidation and its accumulation in the vessel wall during endogenous lipid transport. The atherosclerotic process is initiated by the migration of oxidized LDL to the intima, the release of proinflammatory cytokines, and the development of foam cells (Jebari-Benslaiman et al. 2022). Therefore, avoiding the development of atherosclerosis requires inhibiting de novo cholesterol synthesis, reducing dietary cholesterol consumption, and raising overall antioxidant capacity. Because *Morus nigra* has a high capacity for antioxidants, it protects against LDL oxidation.

Sukandar et al. (2016) found a significant reduction in triglyceride, LDL cholesterol, and total cholesterol levels throughout the study after giving ethanolic extracts of *Morus nigra* leaves (200 mg/kg) to rats induced with 10 mg/kg and propylthiouracil and 200 mg/kg cholesterol in addition to a high-fat diet for 30 days for 21 days. In streptozotocin-induced rats, the hexane fraction of *Morus nigra* leaves (400 mg/kg) was also shown to lower total cholesterol levels; this effect was linked to an increase in insulin sensitivity (Silva et al. 2021). In a different study, rats given 300 mg/kg of an extract from *Morus nigra* leaves were given Triton-X-100, and the results showed a significant reduction in the levels of triglycerides, LDL cholesterol, and total cholesterol (Singh et al. 2023). In another study, the antihyperlipidemic effects of *Morus nigra* leaves were reported to be related to the regulation of PPAR-γ target genes and the inhibition of endogenous cholesterol synthesis by flavonoids (Khawani et al. 2023). *Morus nigra* leave extracts suppressed the development of atherosclerosis in atherosclerotic rats by regulating abnormal lipid metabolism, enhancing anti-oxidative activities, and reducing arterial atherosclerotic lesions which could be attributed to anthocyanins or the cooperative action of anthocyanins, polyphenols, and flavonoids (Jiang et al. 2017). According to Chaudhry et al. (2021), *Morus nigra* shows that possesses antihypertensive activity with concentration-dependent vaso-relaxant effect predominantly mediated through endothelial-independent calcium channel blocking pathways accompanied by partial involvement of endothelium-dependent Nitric Oxide Synthase (NOS) mediated relaxation. Also, *Morus nigra* fruit polyphenols have been shown to modulate gut microbiota and their metabolites and reduce the incidence of cardiovascular disease (Iqbal et al. 2022). In addition, it has been documented that in C57BL/6 J mice given a high-fat diet, dried *Morus alba* fruits at doses of 100 mg/kg and 300 mg/kg lower the risk factors linked to dyslipidemia, avoid weight gain, hepatic and visceral fat accumulation, and shield against myocardial infarction by enhancing cardiac hypertrophy and vascular fibrosis (Chaiwong et al. 2021). The fact that anthocyanins were linked to this impact raises the possibility that *Morus nigra* has a comparable effect.

Organ protective effect

DNA damage is caused by various factors such as elevated caspase activity from drugs, toxins, and inflammatory cytokines, high concentration of free fatty acids in the cell, endoplasmic reticulum stress from alcohol consumption, and oxidative stress from reactive oxygen species (ROS) and reactive nitrogen species (RNS) released from cell metabolism. Fibrogenesis and tissue-organ damage are brought on by the induction of necroptosis and apoptosis following DNA degradation (Ghorbani and Hooshmand 2021). By lowering the amount of free fatty acids, blocking intracellular signaling pathways, and suppressing oxidative stress, the body's antioxidant enzyme capacity, such as SOD, catalase, and peroxidase, as well as the presence of dietary antioxidant flavonols, phenolic compounds, and anthocyanins have a protective effect against DNA damage in the cell (Gulcin 2020; Khoo et al. 2017). *Morus nigra* seeds, branches, leaves and fruits rich in phenolic compounds and anthocyanins show high antioxidant activity and are effective in reducing the level of plasma free fatty acids. Therefore, *Morus nigra* has hepatoprotective, cardioprotective, nephroprotective, neuroprotective, renal-protective and gastro-protective effects (Lim and Choi 2019).

In a study conducted on Wistar rats, it was said that *Morus nigra* fruits extracted with 80% methanol had a protective effect against liver lipid peroxidation

thanks to their antioxidant molecules (Aydin et al. 2015). After CCl4-induced hepatotoxicity in rats for eight weeks, Deniz et al. (2018) administered 150–300 mg/kg of *Morus nigra* extract and found that the extract stopped oxidation of proteins brought on by CCl4. Furthermore, the groups who received *Morus nigra* showed a decrease in the levels of γ glutamyl transferase (GGT) and aspartate amino transferase (AST), as well as an increase in glutathione peroxidase activity and SOD. In a similar study, 150–400 mg/kg *Morus nigra* leaf extract was applied to male albino rats that developed toxicity with Chlorpyrifos and it was stated that it was a safe detoxification agent against organophosphorus intoxication (Seufi et al. 2019). Moreover, Majid et al. (2020) employed 350 mg/kg *Morus nigra* extract for four weeks to protect rats from Diazinon-induced hepatotoxicity, and they observed normal liver morphology along with a noteworthy drop in AST and ALT enzyme levels. Diab et al. (2020) showed the protective effect of *Morus nigra* extracts at doses of 150, 300 and 500 mg/kg against paracetamol-induced testicular, liver and kidney toxicity. According to another study, via regulating inflammatory cytokines, *Morus nigra* extracts given at doses of 500–1000 mg/kg for six weeks prevented hemochromatosis caused by iron overload (Figueredo et al. 2022). In a recent study, Fadil et al. (2023) reported the palliative effect of *Morus nigra* leaf ethanolic extracts (400 mg/kg) on hepatic CYP2E1 and caspase-3 immuno-expression and paracetamol-induced oxidative damage in male rats.

Yiğitaslan et al. (2020) reported that *Morus nigra* extracts increased SOD and glutathione peroxidase activity in rats with 5-Fluorouracil-induced gastrointestinal mucositis and were protective against mucositis. Maqsood et al. (2022) applied 300 mg/kg *Morus nigra* fruit extracts to Sprague Dawley rats that developed hypertension due to verapamil and smoking for 2 months and reported an increase in HDL cholesterol levels, a decrease in serum lipid profile, liver transaminase enzymes and lactate dehydrogenase enzyme levels at the end of the study. In histopathological examination, mild normalization of cardiac myocytes with central nuclei, branching and cross-striations was detected. According to Chaudhry et al. (2021), endothelium-independent calcium channel blockade pathways were primarily responsible for the antihypertensive activity of the aqueous fraction of *Morus nigra* (100–300 mg/kg), while endothelium-independent NOS-mediated relaxation also played a role. Akay et al. (2024) reported that fructose induced advanced glycation end product development in pBR322 DNA, causing oxidative damage, and that *Morus nigra* extracts had a protective effect against DNA damage by scavenging free radicals. According to Yıldız-Gülay and Gülay (2023), male New Zealand white rabbits' spermatological parameters are protected by *Morus nigra* fruits. In a different study, the protective effects of flavonoids from *Morus nigra* leaf extract were observed for intestinal microbiota disturbance, inflammatory response, and liver oxidative stress in *Monopterus albus* caused by excessive carbohydrate intake (Shi et al. 2022). In addition, the neuroprotective (Cásedas et al. 2024; Dalmagro et al. 2017; Turgut et al. 2016), nephroprotective (Hassanalilou et al. 2017; Rahimi-Madiseh et al. 2016) effects of *Morus nigra* and its positive effects on the female reproductive system (Cavalcante et al. 2018; de Queiroz et al. 2012) have been demonstrated in recent studies.

Antibacterial and antifungal effect

Interest in antibacterial chemicals derived from natural sources has grown recently as a result of gram-positive and gram-negative bacteria being resistant to antibiotics. Antibacterial properties can be found in secondary metabolites derived from the fruits, branches, leaves, and seeds of *Morus nigra*. A summary of research findings from the past ten years is provided in Table 5.

In vitro fermentation features

The positive health effects of secondary metabolites found in the seeds, branches, leaves and fruits of *Morus nigra* have been shown in many studies (Liu et al. 2021; Khawani et al. 2023; Khadivi et al. 2024). *Morus nigra* extracts, especially those with antioxidant, anti-inflammatory and antimicrobial effects, are used in traditional and modern medicine. However, these metabolites, which have unstable structures such as anthocyanidins, lose their properties in the gut (Vidana Gamage et al. 2022). Encapsulation techniques and fermentation applications are frequently preferred methods to give anthocyanins stability (Cheng et al. 2023). Fermented foods have a high consumer preference because they contain beneficial

lactic acid bacteria and probiotics with health benefits. There are studies showing that the bioavailability of secondary metabolites increases as a result of fermentation. For example; Chew et al. 2022) reported that effect of *Morus alba* leaf extract fortification and probiotic fermentation on the bioactivities of cottage cheese, and recommended that *Morus alba* leaf extract fortification with *L. plantarum* TAR4 fermentation was the best approach to improve nutrition value. Ai et al. (2022) investigated the structural characterization and in vitro fermentation patterns of polysaccharides found in *Morus nigra* fruit. The change dynamics during in vitro fermentation showed that water extracts of *Morus nigra* fruit could be degraded and consumed by human fecal microbiota, and also showed different degrees of fermentability. Water extracts of *Morus nigra* fruit stimulated the growth of *Bacteroidetes* and *Firmicutes*, inhibited the growth of *Fusobacteria* and *Proteobacteria*, and induced the production of short-chain fatty acids (SCFAs). Another study, it was shown that *Morus nigra* fruit juices fermented with different *lactobacillus* strains and B. *animalis* positively affected the antioxidant effects (Mingshan et al. 2022). In the similar study, it was reported that lactic acid fermentation of *Morus nigra* fruits significantly increased total phenolics, total flavonoids and antioxidant capacities (Wang et al. 2022a, b, c). Current study, the effects of enzymatic treatments (pectinase, pectin lyase and cellulase) on the in vitro digestive and fermentation properties of juice obtained from *Morus nigra* were investigated. The results revealed that enzymatic treatments enhanced the solubilization of carbohydrates from *Morus nigra* fruits, with pectinase showing the most significant effect. Throughout the process of in vitro digestion, there was a gradual increase in the percentage of solubilized carbohydrates from the mulberry juice substrate (Luo et al. 2024).

Other health effects of *Morus nigra*

Morus nigra secondary metabolites come to the fore with their antioxidant, anti-inflammatory, and antibacterial effects, as well as anticancer, antinociceptive (Ali et al. 2023; Ribeiro et al. 2019), antidiarrheal (Akhlaq et al. 2016), anti-melanogenic (de Freitas et al. 2016), anti-Parkinson (Siddique et al. 2023), anti-depressant-like (Merida et al. 2024), anticonvulsant (Zehra et al. 2021), discoloration in dental composites (Çelik et al. 2023) and protective effects against Alzheimer's disease (Cásedas et al. 2024). According to Turan et al. (2017), extracts of *Morus nigra* fruit with dimethyl sulfoxide stopped PC-3 cells' cell cycle in the G1 phase and caused apoptosis by raising caspase activity and lowering mitochondrial membrane potential. Zoofishan et al. (2018) emphasized that morusin, the major component found in *Morus nigra* roots, has strong antitumor properties. Kul and Tüzün (2023) reported the protective effect of Benzothiazole and Ethyllinolenate found in *Morus nigra* extract against prostate cancer proteins. Almutairi et al. (2023) showed anticancer effects of dried *Morus nigra* leaf extract on human breast adenocarcinoma cell lines, human hepatoma, human colorectal carcinoma and human umbilical vein endothelial cells. Gao et al. (2024) reported that *Morus nigra* leaf powders increased the levels of *lactobacillus* and *turicibacter*, suppressed the levels of bacteroides, maintained gastrointestinal stability, and prevented the development of hepatocellular carcinoma by suppressing oxidative damage in liver cells. In a similar study, potential effects were shown on the human colorectal adenocarcinoma cell line HT-29 and the human breast cancer cell line (MCF-7) (Ahmed et al. 2016; Çakıroğlu et al. 2017).

Pharmacokinetics and drug interactions of metabolites of *Morus nigra*

Pharmacokinetics refers to the entire process of a secondary metabolite's absorption, distribution, metabolism, and excretion after entering the body (Donovan et al. 2006). Secondary metabolites and drugs taken into the body by enteral or parenteral routes may interact due to similar chemical structures. This situation is generally called herbal-drug interaction. This interaction can be summarized in general terms as follows. Some of the secondary metabolites and drugs taken into the body by enteral routes undergo pre-systemic elimination. Moreover, carrier proteins such as p-glycoprotein (P-Gp) and organic anion transporting polypeptide (OATP) are involved in the uptake of these compounds into cells and their clearance from cells. While secondary metabolites and drugs taken orally are taken into enterocytes with OATP in the gastrointestinal system, they are metabolized by the cytochrome P 450 (CYP450) enzyme family, which is also found here. P-Gp plays a role in the removal of

some of the secondary metabolites and drugs and the waste products (drug metabolites) released as a result of metabolism from the body. Drugs and secondary metabolites that enter the body parenterally or after pre-systemic elimination are transported to extrahepatic tissues in the bloodstream either free or attached to carrier proteins like albumin. CYP450 is involved in Phase I reactions, which metabolize secondary metabolites, while conjugation with conjugation agents is involved in Phase II reactions, which metabolize medications that are taken into the body. Drugs and their metabolized secondary metabolites are eliminated from the body through the kidney, skin, or lungs in the case of volatile chemicals (Hedaya 2012). Due to the formation of insoluble compounds between secondary metabolites and drugs, their competitive competition during the absorption and excretion stages, the activation or inactivation of CYP450 enzymes, their binding affinity to carrier proteins, and changes in their free concentrations in the blood, the therapeutic effects of secondary metabolites and drugs may be lost, reduced, or toxic effects may occur.

In pharmacokinetic investigations, flavonoids, the primary secondary metabolites of *Morus nigra*, have received the greatest attention. Once microorganisms in the gastrointestinal lumen hydrolyze flavonoid glycosides like rutin and isoquercitrin, glycone is produced (Manach and Donovan 2004). After absorption, flavonoids are metabolized in the liver and small intestine's epithelial cells via first-pass phase II metabolism. In plasma, methyl, glucuronate, and sulfate group conjugated types of metabolites are the most common forms (He et al. 2013). Although the biotransformation of anthocyanins is not fully understood, maximum plasma concentrations have been reported to be 1–100 mmol/L (Ghorbani and Hooshmand 2021). Kim et al. (2006) reported that *Morus nigra* fruit juice inhibits the activity of CYP450 3A, which is involved in the metabolism of many drugs such as antibiotics, antiarrhythmics, benzodiazepines in the liver. In a similar study, it was reported that flavonoids such as quercetin and rutin found in *Morus alba* leaves inhibit P-Gp and CYP 3A4 (Hsu et al. 2013).

Toxicity of *Morus nigra*

While secondary metabolites from *Morus nigra's* roots, branches, leaves, and fruits may be helpful to the human body, there's some risk that high dosages could be toxic. When taken as fruit, risks are unlikely to happen, but when taken as a nutraceutical in large dosages, there is a greater chance of adverse effects. Da et al. (2011) reported that 2000 mg/kg intraperitoneal and 5000 mg/kg oral *Morus nigra* leaf extracts did not cause mortality and had no toxic effects. Souza et al. (2017) reported that *Morus nigra* leaf extracts (50 µg/mL) did not show cytotoxic effects on ovarian, brain and colon tumor cells. Oral administration of 500–1000 mg/kg *Morus nigra* leaf extracts for 28 days did not result in any harmful consequences, according to Figueredo et al. (2018). Yılmaz et al. (2019) reported that *Morus nigra* fruit juice did not cause genotoxicity in human lymphocytes and was protective against genomic changes caused by mitomycin C. However, in one study, a significant increase in serum AST and ALT levels was reported in normal and diabetic mice given 100 mg/kg *Morus nigra* leaf extract twice daily for 42 days (Hemati et al. 2010). A 90-day sub-chronic toxicity study of *Morus alba* extracts reported a NOAEL value of 4200 mg/kg, corresponding to 1058.5 mg/kg anthocyanin equivalents. (Hong et al. 2021). However, Fauzi et al. (2024) reported that there was moderate hepatocellular necrosis and an increase in AST/ALT enzyme levels at doses of 250–1000 mg/kg, and 125 mg/kg of *Morus nigra* leaf extract was the dose that did not cause any side effects. It is estimated that the toxic effects are due to kaempferol and chlorogenic acid. Sood et al. (2024) reported that 2000 mg/kg of orally taken *Morus alba* fruit extracts is the maximum safe dose. Although these studies were not conducted on *Morus nigra*, the presence of secondary metabolites in *Morus nigra* indicates the risk of toxic effects. Since the factors that may cause toxicity originate from secondary metabolites and secondary metabolites are found in different proportions in *Morus* species collected from different climatic regions, more studies on safe intake levels and toxicity are needed.

Conclusions

One of the three most prevalent species in the *Morus* genus of the *Moraceae* family is *Morus nigra*. Its ability to withstand a variety of weather conditions makes it easy to cultivate in many parts of the world. Since ancient times, seeds, branches, leaves and fruits

of *Morus nigra* has been utilized in traditional medicine because of its abundant primary and secondary metabolites. Although *Morus nigra* is rich in nutritional composition, only its fruit is included in the diet. Extracts of its seeds, branches and leaves are consumed as nutraceuticals. Because of its rich in anthocyanins, which give *Morus nigra* its color, it possesses potent antibacterial, anti-inflammatory, and antioxidant properties. In addition, *Morus nigra*, rich in other secondary metabolites such as phenolic compounds and organic acids, stands out with its health effects such as antioxidant, antimicrobial, anti-inflammatory, organ-protective, and antidiabetic, anti-hyperlipidemic. Owing to these benefits, it is utilized as a nutraceutical in the management and avoidance of numerous degenerative chronic illnesses. Studies conducted in the last decade have shown that it also has positive effects on neurological diseases. Since *Morus nigra* fruit contains high levels of simple sugars such as fructose, it is not possible to obtain the positive health effects of *Morus nigra* by consuming its fruit. Exceeding the daily fruit portions required in the diet also causes the simple sugar intake recommended in the diet to be exceeded. Therefore, in order to obtain the positive health effects of *Morus nigra*, it should be taken as a nutraceutical rather than consumed as a fruit. At the same time, there aren't enough research demonstrating its harmful consequences in addition to these possible health concerns. Research demonstrating the usefulness of secondary metabolites in the management of novel and diverse diseases, as well as indicating appropriate dosages for consumption, are critical to maintaining long-term health conditions and preserving the *Morus nigra* plant for next generations.

Funding Open access funding provided by the Scientific and Technological Research Council of Türkiye (TÜBİTAK).

Declarations

Conflict of interests The authors have no competing interests to declare that are relevant to the content of this article.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

Abay M, Eruygur N (2021) Investigation of antioxidant activities of fruit leaf and branche extracts of white (*Morus alba* L.) and Black (*Morus nigra* L.) Mulberry Species from Diyarbakır. Türkiye Tarımsal Araştırmalar Dergisi 8(2):177–183. https://doi.org/10.19159/tutad.841557

Abdelnaby ASI, Mewead AA, Gendy ASH, Abdelkader MAI (2021) Landscape use and aesthetical value of surveyed woody ornamental plants in Cairo Festival City—Cairo—Egypt in landscape gardening. Plant Arch. https://doi.org/10.51470/PLANTARCHIVES.2021.v21.no1.014

Ahmad R, Ahmed A (2016) Evaluation of antibacterial activity of *Morus nigra* and Citrus limon. J Ayurvedic Herb Med 2(6):213–217

Ahmed A, Ali M, El-Kholie E, Sherif N, El-Garawani I (2016) Anticancer activity of *Morus nigra* on human breast cancer cell line (MCF-7) the role of fresh and dry fruit extracts. J Biosci Appl Res 2(6):352–361. https://doi.org/10.21608/jbaar.2016.108382

Ai J, Yang Z, Liu J, Schols HA, Battino M, Bao B, Bai W (2022) Structural characterization and in vitro fermentation characteristics of enzymatically extracted black mulberry polysaccharides. J Agric Food Chem 70(12):3654–3665. https://doi.org/10.1021/acs.jafc.1c07810

Akay F, Çeken Toptancı B, İnceören N, Kılız G, Kızıl M (2024) Evaluation of ethanol extract of *Morus nigra* L. as an inhibitory agent for DNA-Advanced glycation end product (DNA-AGEs). Indian J Biochem Biophys 61(2):75–84. https://doi.org/10.56042/ijbb.v61i2.1610

Akhlaq A, Mehmood MH, Rehman A, Ashraf Z, Syed S, Bawany SA, Gilani A, Ilyas M, Siddiqui BS (2016) The prokinetic, laxative, and antidiarrheal effects of <scp> *Morus nigra* </scp>: possible muscarinic, Ca^{2+} channel blocking, and antimuscarinic mechanisms. Phytother Res 30(8):1362–1376. https://doi.org/10.1002/ptr.5641

Ali A, Tahir HM, Azizullah A, Ali S, Summer M, Gormani AH, Nawaz S, Muzamil A (2023) Anti-inflammatory and analgesic potential of hot water extracts of mulberry leaves. J Innov Sci. https://doi.org/10.17582/journal.jis/2023/9.1.120.131

Ali Redha A, Freije A, Kodikara C, Rondanelli M, Aqeel E, Zafar W, Albunni H, Merza H, Khonji A, Aljar M, Perna S (2023) Comparison of fatty acid profile and mineral content of black mulberry (*Morus nigra*), white mulberry (*Morus alba*) and red mulberry (*Morus rubra*) grown in Bahrain. Applied Food Research 3(2):100358. https://doi.org/10.1016/J.AFRES.2023.100358

Aljane F, Sdiri N (2016) Morphological, phytochemical and antioxidant characteristics of white (*Morus alba* L.), Red (*Morus rubra* L.) and Black (*Morus nigra* L.) mulberry fruits grown in arid regions of Tunisia. J New Sci 35(1):1940–1947

Almutairi BO, Alsayadi AI, Abutaha N, Al-Mekhlafi FA, Wadaan MA (2023) [Retracted] evaluation of the anti-cancer potential of *Morus nigra* and *Ocimum basilicum* mixture against different cancer cell lines: an in vitro evaluation. BioMed Res Int. https://doi.org/10.1155/2023/9337763

Alvarez MA (2014) Plant biotechnology for health. Springer Int Publ. https://doi.org/10.1007/978-3-319-05771-2

American Diabetes Association (ADA) (2020) 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. *Diabetes Care, 43*(Supplement_1): S14–S31. https://doi.org/10.2337/dc20-S002

Amirshahrokhi K, Zohouri A (2021) Carvedilol prevents pancreatic β-cell damage and the development of type 1 diabetes in mice by the inhibition of proinflammatory cytokines, NF-κB, COX-2, iNOS and oxidative stress. Cytokine 138:155394. https://doi.org/10.1016/J.CYTO.2020.155394

Ananda RA, Tikader A, Ravindran S, Girish NV, Mukherjee P (2003) Leaf morpho-anatomical variability in mulberry (Morus spp.) Germplasm. Indian J Plant Genetic Resources 16(1):53–58

Araujo CM, de Pádua Lúcio K, Silva ME, Isoldi MC, de Souza GHB, Brandao GC, Schulz R, Costa DC (2015) *Morus nigra* leaf extract improves glycemic response and redox profile in the liver of diabetic rats. Food Funct 6(11):3490–3499. https://doi.org/10.1039/C5FO00474H

Askin B, Türkyılmaz M, Özkan M, Küçüköner E (2022) Changes in anthocyanins and colour of black mulberry (*Morus nigra*) juice during clarification and pasteurization. J Food Meas Charact 16(1):784–792. https://doi.org/10.1007/s11694-021-01198-w

Aulifa DL, Fitriansyah SN, Ardiansyah SA, Wibowo DP, Julata YA, Christy DS (2017) Phytochemical screening, antibacterial activity, and mode of action on *Morus nigra*. Pharmacogn J 10(1):167–171. https://doi.org/10.5530/pj.2018.1.28

Aulifa DL, Haque S, Riasari H, Budiman A (2021) Antibacterial effects of black mulberry (*Morus nigra*) stem bark extract on *Streptococcus mutans*. Res J Pharm Technol. https://doi.org/10.52711/0974-360X.2021.00763

Aydin S, Yilmaz Ö, Gökçe Z (2015) Protective effect of *Morus nigra* L. (Mulberry) fruit extract on the liver fatty acid profile of wistar rats. Pakistan J Zool 47(1):255–261

Babazadeh Darjazi B, Jaimand K (2023) Sugars, total acids and physicochemical characteristics of black mulberry (*Morus nigra*) genotypes. J Med Plants By-Products 12(2):167–173. https://doi.org/10.22092/jmpb.2022.359701.1496

Bahi A, Necib Y, Merouane F, Bouadi H, Boulahrouf K (2016) Antioxidant, anti-inflammatory and antimicrobial properties of new lectins purified from roots of Algerian plants: *Morus nigra*, *Ruta graveolens*, *Cyperus rotundus* and *Pistacia lentiscus*. World J Pharm Res 5(2):39–53

Barbour JR, Read RA, Barnes RL (2008) Morus L.: the woody plant seed manual. Agricul Handbook 727:728–732

Bezerra M, Ribeiro M, Cosme F, Nunes FM (2024) Overview of the distinctive characteristics of strawberry, raspberry, and blueberry in berries, berry wines, and berry spirits. Compr Rev Food Sci Food Saf. https://doi.org/10.1111/1541-4337.13354

Blitek K, Pruchniewicz D, Bąbelewski P, Czaplicka-Pędzich M, Kubus M (2022) Dependence of the distribution and structure of the white mulberry (*Morus alba*) population in wrocław on the intensity of anthropopressure and thermal conditions. Int J Environ Res Public Health 19(2):838. https://doi.org/10.3390/ijerph19020838

Boranbayeva T, Karadeniz F, Yılmaz E (2014) Effect of storage on anthocyanin degradation in black mulberry juice and concentrates. Food Bioprocess Technol 7(7):1894–1902. https://doi.org/10.1007/s11947-014-1296-8

Bozhüyük MR, Pehluvan M, Kaya T, Doğru B (2016) Organic acid composition of selected mulberry genotypes from Aras Valley. Atatürk Üniv Ziraat Fakültesi Dergisi 46(2):69–74

Budiman A, Aulifa DL (2020) Antibacterial activity and mode of action of black mulberry (*Morus nigra*) fruits extract against *Streptococcus mutans*. Pharmacogn J 12(6s):1722–1726. https://doi.org/10.5530/pj.2020.12.233

Buğrut A, Ada M, Bilgin ÖF, Kafkas NE (2023) Aroma compounds and chemical content of four selected mulberry genotypes using gas chromatography (gc-ms) in Turkey. Int J Agric Forestry Life Sci 7(2):30–32

Çakıroğlu E, Uysal T, Çalıbaşı Koçal G, Aygenli F, Baran G, Baskın Y (2017) The role of *Morus nigra* extract and its active compounds as drug candidate on human colorectal adenocarcinoma cell line HT-29. Int J Clin Oncol Cancer Res 2(1):10–14

Calín-Sánchez Á, Martínez-Nicolás JJ, Munera-Picazo S, Carbonell-Barrachina ÁA, Legua P, Hernández F (2013) Bioactive compounds and sensory quality of black and white mulberries grown in Spain. Plant Foods Hum Nutr 68(4):370–377. https://doi.org/10.1007/s11130-013-0382-9

Can A, Kazankaya A, Orman E, Gundogdu M, Ercisli S, Choudhary R, Karunakaran R (2021) Sustainable mulberry (*Morus nigra* L., *Morus alba* L. and *Morus rubra* L.) production in eastern Turkey. Sustainability 13(24):13507. https://doi.org/10.3390/su132413507

Cásedas G, Moliner C, Abad-Longas A, Núñez S, Gómez-Rincón C, Maggi F, López V (2024) Black mulberries (*Morus nigra* L.) modulate oxidative stress and beta-amyloid-induced toxicity, becoming a potential neuroprotective functional food. Foods 13(16):2577. https://doi.org/10.3390/foods13162577

Cavalcante A, Lins T, Santos J, Barros V, Monte A, Barberino R, Almeida J, Matos M (2018) Supplemented *Morus nigra* extract-based medium associated with <scp>FSH</scp> enables the survival and growth of isolated ovine secondary ovarian follicles. Reprod Domest Anim 53(2):423–432. https://doi.org/10.1111/rda.13122

Çelik ZC, Elbek Çubukçu Ç, Baatmaz SG (2023) Exploring the discoloration potential of Propolis extract and *Morus nigra* syrup on restorative dental composites: an in vitro study. J Health Sci Med 6(2):289–293. https://doi.org/10.32322/jhsm.1217542

Chaiwong S, Chatturong U, Chanasong R, Deetud W, To-on K, Puntheeranurak S, Chulikorn E, Kajsongkram T, Raksanoh V, Chinda K, Limpeanchob N, Trisat K, Somran J, Nuengchamnong N, Prajumwong P, Chootip K (2021) Dried mulberry fruit ameliorates cardiovascular and liver histopathological changes in high-fat diet-induced

hyperlipidemic mice. J Tradit Complement Med 11(4):356–368. https://doi.org/10.1016/j.jtcme.2021.02.006

Chaudhry MA, Mushtaq MN, Alqarni AO, Alyami BA, Mahnashi MH, Alqahtani YS, Akram M, Irfan HM, Riaz H, Qasim S (2021) Endothelium independent calcium channel blocking pathways mediate antihypertensive effect of *Morus nigra*. Pak J Pharm Sci 34(2):781–785

Chen H, Pu J, Liu D, Yu W, Shao Y, Yang G, Xiang Z, He N (2016) Anti-inflammatory and antinociceptive properties of flavonoids from the fruits of black mulberry (*Morus nigra* L.). PLOS ONE 11(4):e0153080. https://doi.org/10.1371/journal.pone.0153080

Chen H, Yu W, Chen G, Meng S, Xiang Z, He N (2017) Antinociceptive and antibacterial properties of anthocyanins and flavonols from fruits of black and non-black mulberries. Molecules 23(1):4. https://doi.org/10.3390/molecules23010004

Cheng X, Zhu J, Chen Z, Wu Z, Zhang F, Wu C, Fan G (2023) Color stability and degradation kinetics of anthocyanins in mulberry stirred yoghurt fermented by different starter cultures. Food Sci Biotechnol 32(10):1351–1359. https://doi.org/10.1007/s10068-023-01271-8

Chew HC, Tang PL, Tan XY, Tan HY (2022) Effect of mulberry leaf extract fortification and probiotic fermentation on the bioactivities of cottage cheese. J Food Meas Charact. https://doi.org/10.1007/s11694-021-01174-4

Chiocchio I, Mandrone M, Tomasi P, Marincich L, Poli F (2021) Plant secondary metabolites: an opportunity for circular economy. Molecules 26(2):495. https://doi.org/10.3390/molecules26020495

Cüce M (2024) Şebinkarahisar'da yetiştirilen karadut odun çeliklerinin köklenmesi üzerine farkli oksin çeşitlerinin etkisi. Karadeniz Fen Bilimleri Dergisi 14(1):304–314. https://doi.org/10.31466/kfbd.1405361

Da JRG, Almeida S, Guimarães AL, Oliveira APD, Da EC, Araújo C, Silva FS, Neves LF, Oliveira RAD, De Sá PGS, Quintans-Júnior LJ (2011) Evaluation of hypoglycemic potential and pre-clinical toxicology of *Morus nigra* L. (Moraceae). Latin Am J Pharm 30(1):96–100

Dadhwal R, Banerjee R (2023) Ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological profile of *Morus alba* L.: a comprehensive review. S Afr J Bot 158:98–117. https://doi.org/10.1016/J.SAJB.2023.05.006

Dalmagro AP, Camargo A, Zeni ALB (2017) *Morus nigra* and its major phenolic, syringic acid, have antidepressant-like and neuroprotective effects in mice. Metab Brain Dis 32(6):1963–1973. https://doi.org/10.1007/s11011-017-0089-y

de Assis Carneiro A, Sinoti SBP, de Freitas MM, Simeoni LA, Fagg CW, de Oliveira Magalhães P, Fonseca-Bazzo YM (2022) Hydroethanolic extract of *Morus nigra* L. leaves: a dual PPAR-α/γ agonist with anti-inflammatory properties in lipopolysaccharide-stimulated RAW 264.7. Plants 11(22):3147. https://doi.org/10.3390/plants11223147

de Pádua Lúcio K, Rabelo ACS, Araújo CM, Brandão GC, de Souza GHB, da Silva RG, de Souza DMS, Talvani A, Bezerra FS, Cruz Calsavara AJ, Costa DC (2018) Anti-inflammatory and antioxidant properties of black mulberry (*Morus nigra* L.) in a model of LPS-induced sepsis. Oxidative Med Cell Longev. https://doi.org/10.1155/2018/5048031

de Paiva Brandão ML, Romano CA, Paz ATS, de Paula JR (2021) What is the impact of research with *Morus nigra*?—a scientometric study. Res Soc Dev 10(2):e49310212838. https://doi.org/10.33448/rsd-v10i2.12838

de Queiroz GT, Santos TR, Macedo R, Peters VM, Leite MN, de Oliveira Guerra M (2012) Efficacy of *Morus nigra* L. on reproduction in female Wistar rats. Food and Chem Toxicol 50(3–4):816–822. https://doi.org/10.1016/j.fct.2011.12.014

de Freitas MM, Fontes PR, Souza PM, William Fagg C, Neves Silva Guerra E, de Medeiros Nóbrega YK, Silveira D, Fonseca-Bazzo Y, Simeoni LA, Homem-de-Mello M, Oliveira Magalhães P (2016) Extracts of *Morus nigra* L. leaves standardized in chlorogenic acid, rutin and isoquercitrin: tyrosinase inhibition and cytotoxicity. PLOS ONE 11(9): e0163130. https://doi.org/10.1371/journal.pone.0163130

Deniz G, Laloglu E, Koc K, Nadaroglu H, Geyikoglu F (2018) The effect of black mulberry (*Morus nigra*) extract on carbon tetrachloride-induced liver damage. Arch Biol Sci 70(2):371–378. https://doi.org/10.2298/ABS171009055D

Dheeb BI, Al-Samarraie MQ (2023) Evaluation of the Antifungal effects of *Glycyrrhiza glabra* L. some pathogenic fungi in vitro. Int J Contemp Appl Rese 10(7)

Diab KA, Fahmy MA, Hassan EM, Hassan ZM, Omara EA, Abdel-Samie NS (2020) Inhibitory activity of black mulberry (*Morus nigra*) extract against testicular, liver and kidney toxicity induced by paracetamol in mice. Mol Biol Rep 47(3):1733–1749. https://doi.org/10.1007/s11033-020-05265-1

Donovan JL, Manach C, Faulks RM, Kroon PA (2006) Absorption and metabolism of dietary plant secondary metabolites. In: Crozier A, Clifford MN, Ashihara H (eds) Plant secondary metabolites: occurrence, structure and role in the human diet. Balckwell Publishing, pp 303–351

El Fadil HA, Behairy A, Ebraheim LLM, Abd-Elhakim YM, Fathy HH (2023) The palliative effect of mulberry leaf and olive leaf ethanolic extracts on hepatic CYP2E1 and caspase-3 immunoexpression and oxidative damage induced by paracetamol in male rats. Environ Sci Pollut Res 30(14):41682–41699. https://doi.org/10.1007/s11356-023-25152-z

Elmasry S, Moawad M (2021) The hepatoprotective effect of gooseberry and black mulberry extracts against carbon tetrachloride-induced liver injury in rats. J Basic Appl Zool 82(1):33. https://doi.org/10.1186/s41936-021-00224-z

Ercisli S (2004) A short review of the fruit germplasm resources of Turkey. Genet Resour Crop Evol 51(4):419–435. https://doi.org/10.1023/B:GRES.0000023458.60138.79

Ercisli S, Orhan E (2007) Chemical composition of white (*Morus alba*), red (Morus rubra) and black (*Morus nigra*) mulberry fruits. Food Chem 103(4):1380–1384. https://doi.org/10.1016/J.FOODCHEM.2006.10.054

Esazadeh K, Ezzati Nazhad Dolatabadi J, Andishmand H, Mohammadzadeh-Aghdash H, Mahmoudpour M, Naemi Kermanshahi M, Roosta Y (2024) Cytotoxic and genotoxic effects of tert-butylhydroquinone, butylated hydroxyanisole and propyl gallate as synthetic food antioxidants. Food Sci Nutr. https://doi.org/10.1002/fsn3.4373

Eyduran SP, Ercisli S, Akin M, Beyhan O, Gecer MK, Eyduran E, Erturk YE (2015) Organic acids, sugars, vitamin C, antioxidant capacity and phenolic compounds in fruits of white (*Morus alba* L.) and black (*Morus nigra* L.) mulberry genotypes. J Appl Botany Food Qual 88:134–138

Fauzi A, Kifli N, Noor MHM, Hamzah H, Azlan A (2024) Bioactivity, phytochemistry studies and subacute in vivo toxicity of ethanolic leaf extract of white mulberry (*Morus alba* Linn.) in female mice. J Ethnopharmacol 325:117914. https://doi.org/10.1016/j.jep.2024.117914

Feng R-Z, Wang Q, Tong W-Z, Xiong J, Wei Q, Zhou W-H, Yin Z-Q, Yin X-Y, Wang L-Y, Chen Y-Q, Lai Y-H, Huang H-Y, Luo Q-L, Wang L, Jia R-Y, Song X, Zou Y-F, Li L-X (2015) Extraction and antioxidant activity of flavonoids of *Morus nigra*. Int J Clin Exp Med 8(12):22328–22336

Figueredo KC, Guex CG, Reginato FZ, Haas da Silva AR, Cassanego GB, Lhamas CL, Boligon AA, Lopes GHH, de Freitas Bauermann L (2018) Safety assessment of *Morus nigra* L. leaves: acute and subacute oral toxicity studies in Wistar rats. J Ethnopharmacol 224:290–296. https://doi.org/10.1016/J.JEP.2018.05.013

Figueredo KC, Guex CG, da Silva ARH, Lhamas CL, Engelmann AM, Maciel RM, Danesi CC, Duarte T, Duarte MMMF, Lopes GHH, Bauermann LDF (2022) In silico and in vivo protective effect of *Morus nigra* leaves on oxidative damage induced by iron overload. Drug Chem Toxicol 45(6):2814–2824. https://doi.org/10.1080/01480545.2021.1991946

Flieger J, Flieger W, Baj J, Maciejewski R (2021) Antioxidants: classification, natural sources, activity/capacity measurements, and usefulness for the synthesis of nanoparticles. Materials 14(15):4135. https://doi.org/10.3390/ma14154135

Gao Q, Chen N, Li B, Zu M, Ma Y, Xu H, Zhu Z, Reis RL, Kundu SC, Xiao B (2024) Natural lipid nanoparticles extracted from *Morus nigra* L. leaves for targeted treatment of hepatocellular carcinoma via the oral route. J Nanobiotechnol 22(1):4. https://doi.org/10.1186/s12951-023-02286-3

Ghanem SM, Salama MM, Zaghlool AN, Kadry MM, Hassanin AM, Haggag MI (2022) Utilization of Egyptian mulberry fruits to improvement the physicochemical and nutritional properties of ice milk. Int J Health Sci. https://doi.org/10.53730/ijhs.v6nS9.12420

Ghorbani A, Hooshmand S (2021) Protective effects of Morus nigra and its phytochemicals against hepatotoxicity: a review of preclinical studies. Pharmacology 106(5–6):233–243. https://doi.org/10.1159/000515032

Girish YR, Sharath Kumar KS, Prashantha K, Rangappa S, Sudhanva MS (2023) Significance of antioxidants and methods to evaluate their potency. Mater Chem Horiz 2(2):93–112. https://doi.org/10.22128/mch.2023.647.1037

Güçer Öz Y, Naharcı Mİ, Çelebi F, Rakıcıoğlu N, Göktaş Z (2024) The effect of black mulberry (*Morus nigra*) consumption on cognition in patients with mild-to-moderate Alzheimer's dementia: a pilot feasibility study. Geriatr Nurs 55:229–236. https://doi.org/10.1016/J.GERINURSE.2023.11.014

Gulcin I (2020) Antioxidants and antioxidant methods: an updated overview. Archives of Toxicology 94(3):651–715. https://doi.org/10.1007/s00204-020-02689-3

Gundogdu M, Muradoglu F, Sensoy RIG, Yilmaz H (2011) Determination of fruit chemical properties of *Morus nigra* L., *Morus alba* L. and *Morus rubra* L. by HPLC. Sci Hortic 132(1):37–41. https://doi.org/10.1016/J.SCIENTA.2011.09.035

Gundogdu M, Canan I, Gecer MK, Kan T, Ercisli S (2017) Phenolic compounds, bioactive content and antioxidant capacity of the fruits of mulberry (Morus spp.) germplasm in Turkey. Folia Hortic 29(2):251–262. https://doi.org/10.1515/fhort-2017-0023

Gundogdu M, Tuncturk M, Berk S, Sekeroglu N, Gezici S (2018) Antioxidant capacity and bioactive contents of mulberry species from eastern anatolia region of Turkey. Indian J Pharm Educ Res 52(4s):s96–s101. https://doi.org/10.5530/ijper.52.4s.82

Hago S, Mahrous EA, Moawad M, Abdel-Wahab S, Abdel-Sattar E (2021) Evaluation of antidiabetic activity of *Morus nigra* L. and *Bauhinia variegata* L. leaves as Egyptian remedies used for the treatment of diabetes. Nat Product Res 35(5):829–835. https://doi.org/10.1080/14786419.2019.1601094

Halberstein RA (2005) Medicinal plants: historical and cross-cultural usage patterns. Ann Epidemiol 15(9):686–699. https://doi.org/10.1016/J.ANNEPIDEM.2005.02.004

Hao J, Gao Y, Xue J, Yang Y, Yin J, Wu T, Zhang M (2022) Phytochemicals, pharmacological effects and molecular mechanisms of mulberry. Foods 11(8):1170. https://doi.org/10.3390/foods11081170

Hassanalilou T, Payahoo L, Shahabi P, Abbasi MM, Jafar-Abadi MA, Bishak YK, Khordadmehr M, Esnaashari S, Barzegar A (2017) The protective effects of *Morus nigra* L. leaves on the kidney function tests and histological structures in streptozotocin-induced diabetic rats. Biomed Res 28(14):6113–6118

He J, Feng Y, Ouyang HZ, Yu B, Chang YX, Pan GX, Dong GY, Wang T, Gao XM (2013) A sensitive LC–MS/MS method for simultaneous determination of six flavonoids in rat plasma: application to a pharmacokinetic study of total flavonoids from mulberry leaves. J Pharm Biomed Anal 84:189–195. https://doi.org/10.1016/J.JPBA.2013.06.019

Hedaya MA (2012) Basic pharmacokinetics, 2nd edn. CRC Press

Hemati A, Jalali MT, Rashidi I, Kalantar HT (2010) Impact of aqueous extract of black mulberry (*Morus nigra*) on liver and kidney funcion of diabetic mice. J Nat Pharm Prod 5(1):18–25

Hong M, Lu M, Qian Y, Wei L, Zhang Y, Pan X, Li H, Chen H, Tang N (2021) A 90-day sub-chronic oral toxicity assessment of mulberry extract in sprague dawley rats. J Health Care Organ Provis Financ. https://doi.org/10.1177/00469580211056044

Hsu P-W, Shia C-S, Lin S-P, Chao P-DL, Juang S-H, Hou Y-C (2013) Potential risk of mulberry-drug interaction: modulation on p-glycoprotein and cytochrome P450 3A. J Agric Food Chem 61(18):4464–4469. https://doi.org/10.1021/jf3052384

Huo J, Ni Y, Li D, Qiao J, Huang D, Sui X, Zhang Y (2023) Comprehensive structural analysis of polyphenols and their

enzymatic inhibition activities and antioxidant capacity of black mulberry (*Morus nigra* L.). Food Chem. 427:136605. https://doi.org/10.1016/j.foodchem.2023.136605

Imran M, Khan H, Shah M, Khan R, Khan F (2010) Chemical composition and antioxidant activity of certain Morus species. J Zhejiang Univ Sci B 11(12):973–980. https://doi.org/10.1631/jzus.B1000173

Iqbal AZ, Javaid N, Hameeda M (2022) Synergic interactions between berry polyphenols and gut microbiota in cardiovascular diseases. Mediterr J Nutr Metab 15(4):555–573. https://doi.org/10.3233/MNM-220071

Islamova FI (2022) Antioxidant activity and biochemical composition of *Morus alba* and *Morus nigra* species. Sel'skokhozyaistvennaya Biol 57(1):122–130. https://doi.org/10.15389/agrobiology.2022.1.122eng

Jan B, Parveen R, Zahiruddin S, Khan MU, Mohapatra S, Ahmad S (2021) Nutritional constituents of mulberry and their potential applications in food and pharmaceuticals: a review. Saudi J Biol Sci 28(7):3909–3921. https://doi.org/10.1016/j.sjbs.2021.03.056

Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, Benito-Vicente A, Martín C (2022) Pathophysiology of atherosclerosis. Int J Mol Sci 23(6):3346. https://doi.org/10.3390/ijms23063346

Jiang Y, Dai M, Nie WJ, Yang XR, Zeng XC (2017) Effects of the ethanol extract of black mulberry (*Morus nigra* L.) fruit on experimental atherosclerosis in rats. J Ethnopharmacol 200:228–235. https://doi.org/10.1016/j.jep.2017.02.037

Junior IDS, Barbosa HDM, Carvalho DC, Barros RDA, Albuquerque FP, Da Silva DHA, Souza GR, Souza NAC, Rolim LA, Silva FMM, Duarte GIBP (2017) Brazilian *Morus nigra* attenuated hyperglycemia, dyslipidemia, and prooxidant status in alloxan-induced diabetic rats. Sci World J 2017:1–10. https://doi.org/10.1155/2017/5275813

Khadivi A, Goodarzi S, Naeemyan F (2024) Fruit quality characteristics and bioactive compounds of *Morus alba* L. var. nigra, Black Mulberry (*Morus nigra* L.), White Mulberry (*Morus alba* L.), Seedless Barberry (*Berberis vulgaris* L. var. asperma), Cornelian Cherry (*Cornus mas* L.), *Ziziphus jujuba* Mill., *Ziziphus spina-christi* (L.) Willd., *Prunus microcarpa* Boiss., and Sumac (*Rhus coriaria* L.). Appl Fruit Sci 66(2):731–737. https://doi.org/10.1007/s10341-024-01048-1

Khawani E, Rizwan B, Noreen S (2023) Nutritional composition, bioactive compounds and hypolipidemic effects of mulberry leaves. NUST J Nat Sci. https://doi.org/10.53992/njns.v7i2.101

Khoo HE, Azlan A, Tang ST, Lim SM (2017) Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res 61(1):1361779. https://doi.org/10.1080/16546628.2017.1361779

Kim H, Yoon Y-J, Shon J-H, Cha I-J, Shin J-G, Liu K-H (2006) Inhibitory effects of fruit juices on CYP3A activity. Drug Metab Dispos 34(4):521–523. https://doi.org/10.1124/dmd.105.007930

Kirac FT, Sahingil D, Hayaloglu AA (2024) Isolation and characterization of a new potential source of bioactive peptides: white mulberry (*Morus alba*) fruits and its leaves. Food Chem Adv 4:100597. https://doi.org/10.1016/J.FOCHA.2023.100597

Kolaylı S, Asadov E, Huseynova A, Rahimova S, Kara Y (2024) Phenolic composition and antioxidant properties of black mulberry (*Morus nigra* L.) fruits and leaves. J Wildl Biodiversity 8(2):355–364

Kruthika HS, Rukmangada MS, Naik VG (2023) Genome size, chromosome number variation and its correlation with stomatal characters for assessment of ploidy levels in a core subset of mulberry (Morus spp.) germplasm. Gene 881:147637. https://doi.org/10.1016/J.GENE.2023.147637

Kul İB, Tüzün B (2023) Prostate cancer properties of extract of *Morus nigra* L. Nd Int Conf Front Acad Res 2:26–32

Kumar A, Kumari M, Mazumdar RS, Dhewa T (2015) In vitro antibacterial activity of ethanolic extracts of *Viola serpens* and *Morus nigra* against pathogens isolated from patients suffering from jaundice. World J Pharm Res 4(2):889–898

Kwon H, Pessin JE (2013) Adipokines mediate inflammation and insulin resistance. Front Endocrinol 4:40863. https://doi.org/10.3389/FENDO.2013.00071/BIBTEX

Lawrence MC (2021) Understanding insulin and its receptor from their three-dimensional structures. Mol Metabolism 52:101255. https://doi.org/10.1016/J.MOLMET.2021.101255

Lazar T, Taiz L, Zeiger E (2003) Plant physiology. Ann Botany 91(6):750–751. https://doi.org/10.1093/aob/mcg079

Lim SH, Choi C-I (2019) Pharmacological properties of *Morus nigra* L. (Black Mulberry) as a promising nutraceutical resource. Nutrients 11(2):437. https://doi.org/10.3390/nu11020437

Liu Y, Yang L (2015) Hypoglycemic and hypolipidemic effects of *Morus nigra* leaves on type 2-diabetic mice. Nat Prod Res Dev 27(8):1411–1415

Liu J, Zhou H, Song L, Yang Z, Qiu M, Wang J, Shi S (2021) Anthocyanins: promising natural products with diverse pharmacological activities. Molecules 26(13):3807. https://doi.org/10.3390/molecules26133807

Łochyńska M, Oleszak G (2013) Multi-use of the white mulberry (*Morus alba* L.). Ecol Quest 15(1):91. https://doi.org/10.12775/v10090-011-0040-5

Luo J, Wang Y, Zhao AZ (2019) The complete chloroplast genome of *Morus alba* (Moraceae: Morus), the herbal medicine species in China. Mitochondrial DNA Part B 4(2):2467–2468. https://doi.org/10.1080/23802359.2019.1638328

Luo P, Ai J, Wang Y, Wang S, Schols HA, Smidt H, Tian L (2024) Effects of enzymatic treatment on the in vitro digestion and fermentation patterns of mulberry fruit juice: a focus on carbohydrates. Food Hydrocoll 146:109223. https://doi.org/10.1016/j.foodhyd.2023.109223

Mahmood SK, Abdulla SM, Hassan KI, Mahmood AB (2024) Effect of some processing methods on the physiochmical properties of black mullberry. Euphrates J Agric Sci 16(1):440–451

Majid H, Shahid S, Shakeel S, Ashraf M, Ali MY, Ahsan A (2020) Protective effect of *Morus nigra* leaf extract on diazinon-induced hepatotoxicity in rats. J Islamabad Med Dent Coll 9(3):175–181. https://doi.org/10.35787/jimdc.v9i3.483

Malabadi RB, Kolkar KP, Chalannavar RK (2022) Plant natural pigment colorants-health benefits: toxicity of synthetic or

artificial food colorants. Int J Innov Sci Res Rev 4:3418–3429
Manach C, Donovan JL (2004) Pharmacokinetics and metabolism of dietary flavonoids in humans. Free Radical Res 38(8):771–785. https://doi.org/10.1080/10715760410001727858
Mann A (2021) Making headway with the mysteries of life's origins. Proc Nat Acad Sci. https://doi.org/10.1073/pnas.2105383118
Manzoor S, Qayoom K (2023) *Morus nigra* L. (Black mulberry): a plant with potent medicinal value. S Asian J Agric Sci 3(1):60–63. https://doi.org/10.22271/27889289.2023.v3.i1a.77
Maqsood M, Khan MI, Sharif MK, Faisal MN (2022) Phytochemical characterization of *Morus nigra* fruit ultrasound-assisted ethanolic extract for its cardioprotective potential. J Food Biochem. https://doi.org/10.1111/jfbc.14335
Martins MS, Rodrigues M, Flores-Félix JD, Garcia-Viguera C, Moreno DA, Alves G, Silva LR, Gonçalves AC (2024) The effect of phenolic-rich extracts of *Rubus fruticosus*, *R. ulmifolius* and *Morus nigra* on oxidative stress and caco-2 inhibition growth. Nutrients 16(9):1361. https://doi.org/10.3390/nu16091361
Meizlish ML, Franklin RA, Zhou X, Medzhitov R (2021) Tissue homeostasis and inflammation. Annu Rev Immunol 39(1):557–581. https://doi.org/10.1146/annurev-immunol-061020-053734
Melo RSD, Reis SAGB, Guimarães AL, Silva NDDS, Rocha JM, El Aouad N, Almeida JRGDS (2022) Phytocosmetic emulsion containing extract of *Morus nigra* L. (Moraceae): development, stability study. Antioxid Antibact Activities Cosmet 9(2):39. https://doi.org/10.3390/cosmetics9020039
Memete AR, Timar AV, Vuscan AN, Miere F, Venter AC, Vicas SI (2022) Phytochemical composition of different botanical parts of Morus species, health benefits and application in food industry. Plants 11(2):152. https://doi.org/10.3390/plants11020152
Merida BF, Dos Santos JL, Junges LH, Zeni ALB, Da Silva ES (2024) Antidepressant-like and antioxidant effects of *Morus nigra* L. in rats subjected to the unpredictable chronic mild stress model. Natural Product Res. https://doi.org/10.1080/14786419.2024.2387253
Miljković V, Nikolić G, Mihajlov-Krstev TM, Arsić B (2018) Antibacterial activities of fruits extracts of three mulberry species (*Morus alba* L., *Morus rubra* L. and *Morus nigra* L.) and bilberry (*Vaccinium myrtillus* L.). Acta Med Med 57(03):05–12. https://doi.org/10.5633/amm.2018.0301
Mingshan LV, Aihaiti A, Liu X, Tuerhong N, Yang J, Chen K, Wang L (2022) Development of probiotic-fermented black mulberry (*Morus nigra* L) juice and its antioxidant activity in C2C12 cells. Fermentation 8(12):697. https://doi.org/10.3390/fermentation8120697
Mohammed Bakheet M, Mohssin Ali H, Jalil Talab T (2024) Evaluation of some proinflammatory cytokines and biochemical parameters in pre and postmenopausal breast cancer women. Cytokine 179:156632. https://doi.org/10.1016/J.CYTO.2024.156632
Momeni H, Salehi A, Absalan A, Akbari M (2022) Hydro-alcoholic extract of *Morus nigra* reduces fasting blood glucose and HbA1c% in diabetic patients, probably via competitive and allosteric interaction with alpha-glucosidase enzyme; a clinical trial and *in silico* analysis. J Complement Integr Med 19(3):763–769. https://doi.org/10.1515/jcim-2021-0005
Muir JG, Shepherd SJ, Rosella O, Rose R, Barrett JS, Gibson PR (2007) Fructan and free fructose content of common australian vegetables and fruit. J Agric Food Chem 55(16):6619–6627. https://doi.org/10.1021/jf070623x
Nelson RH (2013) Hyperlipidemia as a risk factor for cardiovascular disease. Primary Care Clin Office Pract 40(1):195–211. https://doi.org/10.1016/j.pop.2012.11.003
Okatan V, Gündeşli MA, Melyanovskaya AYu, Panfilova OV, Krasova NG (2022) Some phytochemicals and sugar contents of black mulberry (<i>Morus nigra</i> L.) genotypes from Simav District, Kütahya Province, Turkey. Proc Appl Bot Genet Breed 183(2):67–73. https://doi.org/10.30901/2227-8834-2022-2-67-73
Othman AA, Aljabary AMAO, Hama HJMDA, Awlqadir FH (2024) Evaluation of chemical, bioactive compounds and minerals of three mulberry species. Int J Agric Biol 31(3):213–217
Özgen M, Serçe S, Kaya C (2009) Phytochemical and antioxidant properties of anthocyanin-rich *Morus nigra* and Morus rubra fruits. Sci Hortic 119(3):275–279. https://doi.org/10.1016/J.SCIENTA.2008.08.007
Padilha MM, Vilela FC, Rocha CQ, Dias MJ, Soncini R, dos Santos MH, Alves-da-Silva G, Giusti-Paiva A (2010) Anti-inflammatory properties of *Morus nigra* leaves. Phytother Res 24(10):1496–1500. https://doi.org/10.1002/ptr.3134
Panchal P, Miller AJ, Giri J (2021) Organic acids: versatile stress-response roles in plants. J Exp Bot 72(11):4038–4052. https://doi.org/10.1093/jxb/erab019
Paunović SM, Mašković P, Milinković M (2020) Determination of primary metabolites, vitamins and minerals in black mulberry (*Morus nigra*) berries depending on altitude. Erwerbs-Obstbau 62(3):355–360. https://doi.org/10.1007/s10341-020-00509-7
Pawlowska AM, Oleszek W, Braca A (2008) Quali-quantitative analyses of flavonoids of *Morus nigra* L. and *Morus alba* L. (Moraceae) fruits. J Agric Food Chem 56(9):3377–3380. https://doi.org/10.1021/jf703709r
Radojkovic M, Zekovic Z, Dojcinovic B, Stojanovic Z, Cvetanovic A, Manojlovic D (2014) Characterization of Morus species in respect to micro, macro, and toxic elements. Acta Periodica Technol 45:229–237. https://doi.org/10.2298/APT1445229R
Rahimi-Madiseh M, Naimi A, Heydarian E, Rafieian-Kopaei M (2016) Renal biochemical and histopathological alterations of diabetic rats under treatment with hydro alcoholic *Morus nigra* extrac. J Renal Injury Prev 6(1):56–60. https://doi.org/10.15171/jrip.2017.10
Rahman M, Islam S (2021) Studies on food, health and environmental perspectives in mulberry (Morus Spp.)—a review. J Bio-Sci. https://doi.org/10.3329/jbs.v29i0.54832
Ren X, Sun Y, Guo Q, Liu H, Jiang H, He X, Li X, Shi X, Xiu Z, Dong Y (2022) Ameliorating effect of the total flavonoids of *Morus nigra* L. on prediabetic mice based on regulation of inflammation and insulin sensitization. J Agric Food Chem 70(39):12484–12501. https://doi.org/10.1021/acs.jafc.2c04970
Ribeiro AEAS, Soares JMD, Silva HAL, de Souza Wanderley CW, Moura CA, de Oliveira-Junior RG, de Oliveira AP, Rolim LA, Costa EV, da Silva Almeida JRG, de Oliveira

HP (2019) Inhibitory effects of *Morus nigra* L. (Moraceae) against local paw edema and mechanical hypernociception induced by *Bothrops jararacussu* snake venom in mice. Biomed Pharmacother 111:1046–1056. https://doi.org/10.1016/j.biopha.2019.01.011

Rodrigues EL, Marcelino G, Silva GT, Figueiredo PS, Garcez WS, Corsino J, Guimarães RDCA, Freitas KDC (2019) Nutraceutical and medicinal potential of the morus species in metabolic dysfunctions. Int J Mol Sci 20(2):301. https://doi.org/10.3390/ijms20020301

Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, Yin X, Xu Q (2023) Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol 14:1161521. https://doi.org/10.3389/FENDO.2023.1161521/BIBTEX

Saeed A, Kauser S, Hussain A, Nadeem AA (2023) Comparative variability of nutrients, minerals, phenolics and anthocyanins with antioxidant potentials during fruit development stages in five Mulberry (Morus) cultivars. J Berry Res. https://doi.org/10.3233/JBR-230053

Sakar E, Ercisli S, Marc RA, Gulen H, Assouguem A, Ullah R, Shahat AA, Bari A, Farah A (2023) Black mulberry (*Morus nigra* L.) fruits: as a medicinal plant rich in human health-promoting compounds. Open Chem. https://doi.org/10.1515/chem-2022-0323

Sánchez-Salcedo EM, Mena P, García-Viguera C, Martínez JJ, Hernández F (2015) Phytochemical evaluation of white (*Morus alba* L.) and black (*Morus nigra* L.) mulberry fruits, a starting point for the assessment of their beneficial properties. J Funct Foods 12:399–408. https://doi.org/10.1016/J.JFF.2014.12.010

Saxena M, Saxena J, Nema R, Singh D, Gupta A (2013) Phytochemistry of medicinal plants. J Pharmacogn Phytochem 1(6):168–182

Serio G, Asteggiano A, Gatti N, La Rosa L, Bertea CM, Farina V, Medana C, Mannino G, Gentile C (2024) Comparative profiling of secondary metabolites and antioxidant properties of twelve Morus varieties: insights into the diversity of *M. alba* and *M. nigra* grown in sicily. Food Biosci 61:104782. https://doi.org/10.1016/j.fbio.2024.104782

Serra D, Paixão J, Nunes C, Dinis TCP, Almeida LM (2013) Cyanidin-3-glucoside suppresses cytokine-induced inflammatory response in human intestinal cells: comparison with 5-aminosalicylic acid. PLoS ONE 8(9):e73001. https://doi.org/10.1371/journal.pone.0073001

Seufi AM, Mohammed HA, Moussa FI, El-Din AAS, El-Saadani M, Taha TH, Hafez EE (2019) Protective effects of the aqueous extract of black mulberry leaves, *Morus nigra*, on chlorpyrifos toxicity in male albino rats. Jordan J Biol Sci 12(4):385–393

Sharifee F, Asadpour L, Shariati S, Salehzadeh A (2022) Evaluation of antibacterial effect of aqueous, hydro-alcoholic and alcoholic extracts of *Morus nigra* on gram-positive and gram-negative bacteria. J Adv Environ Health Res 10(3):225–234. https://doi.org/10.32598/JAEHR.10.3.1259

Shi Y, Zhong L, Fan Y, Zhang J, Zhong H, Liu X, Shao C, Hu Y (2022) The protective effect of mulberry leaf flavonoids on high-carbohydrate-induced liver oxidative stress, inflammatory response and intestinal microbiota disturbance in *Monopterus albus*. Antioxidants 11(5):976. https://doi.org/10.3390/antiox11050976

Shinde A, Ganu J, Naik P (2012) Effect of free radicals and antioxidants on oxidative stress: a review. J Dental Allied Sci 1(2):63. https://doi.org/10.4103/2277-4696.159144

Siddique YH, Ara G, Naz F (2023) Blackberry (*Morus nigra*) usage in Parkinson's disease. In: Treatments, nutraceuticals, supplements, and herbal medicine in neurological disorders, pp 719–734. https://doi.org/10.1016/B978-0-323-90052-2.00005-6

Sies H, Berndt C, Jones DP (2017) Oxidative stress. Annu Rev Biochem 86(1):715–748. https://doi.org/10.1146/annurev-biochem-061516-045037

Silva DH, Barbosa HM, SILVA JF, Moura CA, Gomes DA, Almeida JR, Lira EC (2021) Antidiabetic properties of oral treatment of hexane and chloroform fractions of *Morus nigra* leaves in streptozotocin-induced rats. Anais Da Academia Brasileira de Ciências 93(suppl 4): e20210744. https://doi.org/10.1590/0001-3765202120210744

Singh S, Sengar M, Kushwaha J, Singh D, Tripathi A, Singh D (2023) Hypolipidemic activity of standardized crude leaf extracts of *Morus nigra* L. J Pharm Sci Res 15(5):1086–1091

Skrovankova S, Ercisli S, Ozkan G, Ilhan G, Sagbas HI, Karatas N, Jurikova T, Mlcek J (2022) Diversity of phytochemical and antioxidant characteristics of black mulberry (*Morus nigra* L.) fruits from Turkey. Antioxidants 11(7):1339. https://doi.org/10.3390/antiox11071339

Sood P, Shri R, Singh V, Ahmad SF, Attia SM (2024) Acute oral toxicity and safety assessment of *Morus alba* L. (Moraceae) methanol fruit extract in mice. Italian J Food Sci 36(3):11–19. https://doi.org/10.15586/ijfs.v36i3.2578

Souza GR, Oliveira-Junior RG, Diniz TC, Branco A, Lima-Saraiva SRG, Guimarães AL, Oliveira AP, Pacheco AGM, Silva MG, Moraes-Filho MO, Costa MP, Pessoa CÓ, Almeida JRGS (2017) Assessment of the antibacterial, cytotoxic and antioxidant activities of *Morus nigra* L (Moraceae). Braz J Biol 78(2):248–254. https://doi.org/10.1590/1519-6984.05316

Sukandar EY, Safitri D, Aini NN (2016) THES study of ethanolic extract of binahong leaves (*Anredera cordifolia* (TEN.) steenis) and mulberry leaves (*Morus nigra* L.) in combination on hyperlipidemic induced rats. Asian J Pharm Clin Res 9(6):288. https://doi.org/10.22159/ajpcr.2016.v9i6.14412

Talo Yildirim T, Ozan G, Dundar S, Bozoglan A, Karaman T, Dildes N, Kaya CA, Kaya N, Erdem E (2019) The effects of *Morus nigra* on the alveolar bone loss in experimentally-induced periodontitis. Eur Oral Res. https://doi.org/10.26650/eor.20190021

Tang P, Yang X, Chen H, Zhang T, Tang H, Pang K (2022) Antidiabetic activity of extract from *Morus nigra* L. twigs through activation of AMPK/PKC pathway in mice. J Funct Foods 99:105358. https://doi.org/10.1016/j.jff.2022.105358

Thabti I, Marzougui N, Elfalleh W, Ferchichi A (2011) Antioxidant composition and antioxidant activity of white (*Morus alba* L.), black (*Morus nigra* L.) and red (*Morus rubra* L.) mulberry leaves. Antioxid Compos Acta Botanica Gallica 158(2):205–214. https://doi.org/10.1080/12538078.2011.10516267

Thakur N, Bashir SF, Kumar G (2020) Assessment of phytochemical composition, antioxidant and anti-inflammatory activities of methanolic extracts of *Morus nigra* and *Artocarpus heterophyllus* leaves. Plant Cell Biotechnol Molecular Biol 21(3 & 4):83–91

Tomas M, Toydemir G, Boyacioglu D, Hall R, Beekwilder J, Capanoglu E (2015) The effects of juice processing on black mulberry antioxidants. Food Chem 186:277–284. https://doi.org/10.1016/J.FOODCHEM.2014.11.151

Trak D, Arslan Y (2021) Synthesis of silver nanoparticles using dried black mulberry (*Morus nigra* L.) fruit extract and their antibacterial and effective dye degradation activities. Inorganic Nano-Metal Chem. https://doi.org/10.1080/24701556.2021.1980038

Turan I, Demir S, Kilinc K, Burnaz NA, Yaman SO, Akbulut K, Mentese A, Aliyazicioglu Y, Deger O (2017) Antiproliferative and apoptotic effect of *Morus nigra* extract on human prostate cancer cells. Saudi Pharm J 25(2):241–248. https://doi.org/10.1016/j.jsps.2016.06.002

Turgut NH, Mert DG, Kara H, Egilmez HR, Arslanbas E, Tepe B, Gungor H, Yilmaz N, Tuncel NB (2016) Effect of black mulberry (*Morus nigra*) extract treatment on cognitive impairment and oxidative stress status of <scp>d</scp> -galactose-induced aging mice. Pharm Biol 54(6):1052–1064. https://doi.org/10.3109/13880209.2015.1101476

Twaij BM, Hasan MdN (2022) Bioactive secondary metabolites from plant sources: types, synthesis, and their therapeutic uses. Int J Plant Biol 13(1):4–14. https://doi.org/10.3390/ijpb13010003

Uyak C, Aglar E, Ozturk B, Doğan A, Tekin O (2024) Biochemical characterization of mulberry (Morus spp.) genotypes from the Türkiye (Hizan, Bitlis): a comprehensive analysis of fruit properties and bioactive compounds. Food Sci Nutr. https://doi.org/10.1002/fsn3.4255

Vidana Gamage GC, Lim YY, Choo WS (2022) Sources and relative stabilities of acylated and nonacylated anthocyanins in beverage systems. J Food Sci Technol 59(3):831–845. https://doi.org/10.1007/s13197-021-05054-z

Vijayan K, Tikader A, Weiguo Z, Nair CV, Ercisli S, Tsou C-H (2011) Morus. Wild crop relatives: genomic and breeding resources. Springer, Berlin, pp 75–95. https://doi.org/10.1007/978-3-642-20447-0_5

Vijayan K, Raju PJ, Tikader A, Saratchnadra B (2014) Biotechnology of mulberry (Morus L.)—a review. Emir J Food Agric. https://doi.org/10.9755/ejfa.v26i6.18019

Vukmirović S, Ilić V, Tadić V, Čapo I, Pavlović N, Tomas A, Paut Kusturica M, Tomić N, Maksimović S, Stilinović N (2023) Comprehensive analysis of antioxidant and hepatoprotective properties of *Morus nigra* L. Antioxidants 12(2):382. https://doi.org/10.3390/antiox12020382

Wang L, Yang Y, Liu C, Chen R-Y (2010) Three new compounds from *Morus nigra* L. J Asian Nat Prod Res 12(6):431–437. https://doi.org/10.1080/10286020.2010.489824

Wang RS, Dong PH, Shuai XX, Chen MS (2022a) Evaluation of different black mulberry fruits (*Morus nigra* L.) based on phenolic compounds and antioxidant activity. Foods 11(9):1252. https://doi.org/10.3390/foods11091252

Wang L, Wang J, Ma M, Shen L, Huang T, Huang C, Jia A, Hu X (2022b) Prenylated flavonoids from *Morus nigra* and their insulin sensitizing activity. Phytochemistry 203:113398. https://doi.org/10.1016/j.phytochem.2022.113398

Wang K, Qi J, Jin Y, Li F, Wang J, Xu H (2022c) Influence of fruit maturity and lactic fermentation on physicochemical properties, phenolics, volatiles, and sensory of mulberry juice. Food Biosci 48:101782. https://doi.org/10.1016/j.fbio.2022.101782

Wang Y-A, Liu C, Guo X, Zhang M-Q, Sun S, Sun J-Y, Khan A, Liu L, Chen Y-Y (2023) Natural products and biological activities of plants from genus morus: 2011–2023. Curr Top Med Chem 23(28):2640–2698. https://doi.org/10.2174/0115680266257370230920055003

Xu L, Yu M, Niu L, Huang C, Wang Y, Wu C, Yang P, Hu X (2020) Phenolic compounds isolated from *Morus nigra* and their α-glucosidase inhibitory activities. Nat Prod Res 34(5):605–612. https://doi.org/10.1080/14786419.2018.1491041

Xu X, Liu A, Hu S, Ares I, Martínez-Larrañaga MR, Wang X, Martínez M, Anadón A, Martínez MA (2021) Synthetic phenolic antioxidants: metabolism, hazards and mechanism of action. Food Chem 353:129488. https://doi.org/10.1016/J.FOODCHEM.2021.129488

Yadav S, Nair N, Biharee A, Prathap VM, Majeed J (2022) Updated ethnobotanical notes, phytochemistry and phytopharmacology of plants belonging to the genus Morus (Family: Moraceae). Phytomedicine plus 2(1):100120. https://doi.org/10.1016/J.PHYPLU.2021.100120

Yiğitaslan S, Özkaraman A, Açıkgöz A, Balcı Alparslan G, Toprak Ç, Göger F, Sahin E (2020) *Morus nigra*'nın sıçanlarda 5-florourasil ile oluşturulmuş gastrointestinal mukozite karşı olası tedavi ediciliği. Osmangazi J Med. https://doi.org/10.20515/otd.549371

Yilmaz KU, Zengin Y, Ercisli S, Demirtas MN, Kan T, Nazli AR (2012) Morphological diversity on fruit characteristics among some selected mulberry genotypes from Turkey. J Anim Plant Sci 22(1):211–214

Yılmaz S, Uçar A, Göktaş B (2019) Genotoxic and genoprotective potential of black mulberry (*Morus nigra*) fruit. Anais Da Acad Bras Ciênc. https://doi.org/10.1590/0001-3765201920190337

Zehra T, Sarfaraz S, Ikram R (2021) Dose dependent anticonvulsant activity of *Morus nigra* in strychnine induced seizures model. Pak J Pharm Sci 34(6):2167–2171

Zhang H, Dhalla NS (2024) The role of pro-inflammatory cytokines in the pathogenesis of cardiovascular disease. Int J Mol Sci 25(2):1082. https://doi.org/10.3390/ijms25021082

Zhang R, Zhang Q, Zhu S, Liu B, Liu F, Xu Y (2022) Mulberry leaf (*Morus alba* L.): a review of its potential influences in mechanisms of action on metabolic diseases. Pharmacol Res 175:106029. https://doi.org/10.1016/J.PHRS.2021.106029

Zhang YM, Wei RM, Feng YZ, Zhang KX, Ge YJ, Kong XY, Li XY, Chen GH (2024) Sleep deprivation aggravates lipopolysaccharide-induced anxiety, depression and cognitive impairment: the role of pro-inflammatory cytokines and synaptic plasticity-associated proteins. J Neuroimmunol 386:578252. https://doi.org/10.1016/J.JNEUROIM.2023.578252

Zhao W, Miao X, Jia S, Pan Y, Huang Y (2005) Isolation and characterization of microsatellite loci from the mulberry.

Morus l Plant Sci 168(2):519–525. https://doi.org/10.1016/j.plantsci.2004.09.020

Zhou R, Li D, Kou Q, Jiao Z, Ning Z (2019) Evaluation of anti-inflammatory, antimicrobial and wound healing activity of *Morus nigra*. S Afr J Bot 124:540–545. https://doi.org/10.1016/j.sajb.2019.06.021

Zoofishan Z, Hohmann J, Hunyadi A (2018) Phenolic antioxidants of *Morus nigra* roots, and antitumor potential of morusin. Phytochem Rev 17(5):1031–1045. https://doi.org/10.1007/s11101-018-9565-1

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.