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Pharmacological properties of mulberry fruits and effect of different preservation methods on phytochemical profile: A review

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Abstract
Mulberry is a fast-growing deciduous tree that belongs to the Moraceae family. Mulberry fruits are used in traditional medicine for several years and are known for their ability to improve human health. Mulberry fruits are well-known around the world for their strong flavor, which makes them appropriate for consumption either fresh or as an ingredient in value-added goods and for culinary purposes Mulberry fruit, in addition to having a high nutritional value, has several bioactive phytochemicals that may be related with some potential pharmacological effects including anti-cholesterol, anti-diabetic, antioxidative, and anti-obesity effects. Mulberry fruits are difficult to preserve due to their high water content. To improve mulberry fruit consumption and availability, effective processing processes to keep mulberry fruit fresh must be selected. The most extensively utilized physical methods of fruit preservation are based on temperature-related processes. Methods based on temperature reduction, such as chilling and freezing, as well as those based on a significant increase in temperatures, such as sterilization and pasteurization, are widely used. This review highlights the effect of different preservation methods on the phytochemical profile and pharmacological potential of the mulberry fruit.

Keywords: *Morus* spp., pharmacological, anti-oxidant, anti-hyperlipidemia, vacuum drying, vacuum freeze drying

Introduction
Mulberry is a traditional herb that has been used in medicine for decades due to its chemical composition and pharmacological properties (Sharma *et al*., 2020) [48]. Mulberry (*Morus* spp.) belongs to the genus *Morus* of the Moraceae family and can be found in a wide range of climatic and environmental conditions, from tropical to temperate (Zhang *et al*., 2018) [63]. The genus is widely dispersed in Asia, Europe, South, and North America, as well as in hilly areas of the Himalayas. There are 24 species of Morus with 100 known varieties (Zhang and Ma, 2018) [64]. *Morus alba* (white mulberry), *Morus nigra* (black mulberry), and *Morus rubra* (red mulberry) are the three most commonly found species of genus *Morus*. One of the most common applications for the plant is to raise silkworms, which eat the leaves as their primary source of food (Sarkhel *et al*., 2020) [47]. Mulberry is known in India as "KalpaVruksha" because all parts of the plant are utilized for different purposes, and its fruit is known as toot and shahtoot (King's or "superior" mulberry) (Jan *et al*., 2021) [17]. The fruit can be used directly or in processed product forms, such as juices, syrups, liquors, molasses, jams, wines, and soft beverages (Rohela *et al*., 2020) [46]. Mulberry fruits are known for their ability to improve human health. The Indian ayurveda system of medicine has long used extracts from this plant to treat a variety of illnesses and promote human health (Ghosh *et al*., 2017) [15].
Mulberry fruits are appetizing with a sweet flavor to a tangy-sweet flavor and low in calories (Ma *et al*., 2020) [29]. Mulberry fruits are highly perishable, containing 75-80% water, which causes them to undergo progressive changes and spoilage caused by microbes, moulds, insects, or naturally occurring enzymes. Dried fruits are a good substitute for fresh fruits since they last a long time and make seasonal fruits available all year long (Teng and Lee, 2014) [54]. Drying/dehydration have proven to be a cost effective technique to reduce nutrient losses and microbiological development, extending the shelf life of fruits. However, bioactive compounds like anthocyanin and its antioxidant properties in fruits and vegetables can be altered and often damage during processing (Anonymous, 2018). Drying has become more sophiscated and complex in recent years due to the extensive use of technology and thorough examination and optimization of drying parameters at each stage of the process (Kozlowska *et al*., 2021).

Botanical Description

Mulberry is a fast-growing deciduous or medium-sized woody perennial plant that grows up to 10-15 meters tall (Wani *et al*., 2017) [59]. The plant has a deep root system. Generally, the plants are dioecious. The fruits have an elliptical cylindrical shape with a length of 1-3 cm. There are several tiny achenes on the surfaces. Flowering lasts approximately 4-5 months, while the fruiting lasts about 6-7 months. Generally, the harvesting season lasts from April till June and the best growing temperature is between 24 and 28 °C (Ma *et al*., 2020) [29]. The color of the fruit change from green to red and purple while maturation (Li *et al*., 2020) [26]. The leaves come in a variety of shapes, and sizes, but are usually lobed and are 5 to 7.5 cm long and 6 to 10 cm wide. The leaves have a glossy texture. The color of the flower is yellowish-green. The inflorescence is always auxiliary. Female spikes are ovoid and stalked, whereas male spikes are cylindrical and broad (Acharya *et al*., 2022) [1]. Male flowers are loosely grouped, and the inflorescence dries and falls off after spilling pollen. The female inflorescence is usually short, with compactly placed flowers. Spikes on males are often longer than those on females (Jan *et al*., 2021) [17].

Fig 1: *Morus alba*, *Morus nigra*, *Morus rubra*

Production and consumption scenario at the global level and national level

Mulberry is widely grown in eastern, western, and southeastern Asia, southern Europe, southern North America, and parts of Africa. Mulberry tree commercialization for fruit has just been considered in the last two decades (Ukav, 2018) [57]. The fruit of East Asian white mulberry- a species that has become widely naturalized in eastern North American urban area has a distinct flavor that is sometimes described as refreshing and acidic, with a hint of gumminess (Anonymous, 2017). Mulberry is also commonly seen in China as a paste known as sangshengao. This paste is dissolved in warm water to make a tea that boosts kidney and liver function while also improving vision and hearing (Memete *et al*., 2022) [32]. Mulberries are used to make jellies, sweets, and sauces in Persian culture. Iranians use dehydrated mulberries to sweeten black tea (Rahman and Islam, 2021) [41]. Mulberry syrup and processed mulberry products are commonly consumed in Vietnam (Trung *et al*., 2018) [55]. Mulberry wine is a popular women beverage in Europe (Nazim *et al*., 2017) [34].

Mulberry cultivation is practiced in almost every state in India. Mulberry cultivation is primarily found in the tropical (Karnataka, Andhra Pradesh, and Tamil Nadu) and sub-tropical (West Bengal, Himachal Pradesh, and the North-Eastern) zones of India, as well as some temperate regions (Sarkhel *et al*., 2020) [47]. *Morus indica* is probably the most widely cultivated Morus species. *Morus alba*, popularly known as white mulberry, is a second popular mulberry species. In Himachal Pradesh, Punjab, and Kashmir, this species grows abundantly. Maharashtra and Rajasthan have white mulberries as well (Anonymous, 2014). Mulberries are rarely found in markets, despite their seasonal availability, due to their extreme perishability. However, because of industrial applications that increase the flavor and odor of the fruit, it is consumed in processed forms such as jam, jelly, wine, and juice (Yuan and Zhao, 2017) [62]. Fruits are used to make juice and jam making in central India. The fruits of *Morus alba* are made into juice, liquor, and stews. In Maharashtra, the fruits of the *Morus indica* are used to make jam, jelly, and juice.

Nutritional composition of mulberry fruits

Mulberry fruits are known for their high nutritional value, which makes them beneficial for human health. For a fruit, mulberries are rich in fiber, protein and have a significant amount of potassium, calcium, iron, magnesium, and several other trace minerals (Mandal, 2020) [30]. Mulberry fruit contains nearly all of the essential amino acids required by humans such as valine, tyrosine, phenylalanine, tryptophan, methionine, isoleucine, leucine, lysine, cysteine, histidine, and threonine (Jiang and Nie, 2015) [18]. Linoleic acid, an essential polyunsaturated fatty acid present in mulberry fruits, is the main fatty acid and plays a vital function in human development, health promotion, and illness prevention (Lee *et al*., 2014) [24]. Mulberries are high in vitamin C, vitamin A, and B vitamins (Paunović *et al*., 2020) [37]. The major sugar present in the fruit is glucose, and the major organic acid is malic acid (Eyduran *et al*., 2015) [14].

Polysaccharides, the main active components of mulberry resources, have been shown to have bioactivities such as antioxidant activity, hypoglycemic activity, immunomodulation, and anti-obesity (Rohela *et al*., 2020) [46]. The major active compounds of the mulberry plant are phenols, which are abundant micronutrients in the human diet (Wen *et al*., 2019) [60]. These phenols include resveratrol, oxyresveratrol, chlorogenic acid, mulberroside, moracin, and maclurin (Ramappa *et al*., 2020) [43]. Flavonoids are chemically polyphenolic secondary metabolic chemicals that are found across the green plant kingdom. Kaempferol, rutin, quercetin, and catechins are the typical flavonoid chemicals found in mulberry (Rodrigues *et al*., 2019) [45]. Anthocyanins, type of flavonoid polyphenols that occur naturally and are responsible for the color of mulberry fruit. Mulberry fruit contains the main anthocyanins cyanidin-3-O-glucoside (C_3G), cyanidin-3-O-rutinoside (C_3R), and pelargonidin-3-glucoside (P_3G) (Mandal *et al*., 2020; Hao *et al*., 2022) [30, 16]. Anthocyanins have been shown to have antioxidant, anti-inflammatory, and anti-cancer activity, as well as the ability to improve chronic disorders (Natic *et al*., 2015) [33].

Table 1: Major functional compounds and their functional activities

Functional ingredients	Functionality	References
Polysaccharides	Antioxidant, anti-diabetic, anti-inflammatory, anti-apoptotic, immunostimulatory effect	Liu and Lin, 2014; Chen *et al*., 2018 [28, 8]
Phenols (resveratrol, oxyresveratrol, and chlorogenic acid)	Antibacterial, antioxidant, anti-browning, anti-inflammatory, neuroprotective, anti-hyperlipidemic	Turan *et al*., 2017; Zhang *et al*., 2017 [56, 65]
Anthocyanins (cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside)	Antioxidant, anticancer, anti-inflammatory, anti-diabetic, neuroprotective activity	Chen *et al*., 2016; de Rosas *et al*., 2019 [6, 12]
Flavonoids (Kaempferol, rutin, quercetin, and catechins)	Anti-allergic, antithrombotic, anti-immobility, antiviral, hepatoprotective activity	Ramesh *et al*., 2014; Manzoor *et al*., 2022 [44, 31]

Pharmacological properties of mulberry fruits

Antioxidative potential

Oxidative stress is defined as an imbalance between free radicals and antioxidants that favors radicals. A high quantity of free radicals causes many metabolic changes in organisms, and is a major contributor to a wide range of diseases such as diabetes, atherosclerosis, cardiovascular and neurological diseases, and cancer (Memete *et al*., 2022) [32]. The presence of a diverse range of phytochemicals accounts for the antioxidative capability of the mulberry plant. Mulberries are also high in anthocyanin constituents, which have remarkable antioxidant properties (Eyduran *et al*., 2015) [14] as well as anti-inflammatory, antimicrobial, anti-obesity, anti-diabetic, anti-hyperlipidemic, antihypertensive, cardio protective (reduced risk of coronary heart disease and stroke), and anticancer properties (Lee *et al*., 2017) [25]. Another study found that both mulberry extract and mulberry anthocyanin extract scavenge free radicals, prevent the oxidation of low-density lipoprotein, and lower the atherosclerosis caused on by macrophages (Hao *et al*., 2022) [16].

Resveratrol lowers reactive oxygen species (ROS) levels by inhibiting lipid peroxidation. Mulberry fruits have the highest resveratrol concentration and antioxidant activity when compared to Jamun (*Syzygium cumini*), and Jackfruit (*Artocarpus heterophyllus*) (Shrikanta *et al*. 2015) [49]. Mulberry fruits contain several flavonoids and polyphenols which are associated with antioxidative potential with higher scavenging activity against free radicals such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid), hydroxyls, and superoxide anion radicals (Mandal, 2020; Lim and Choi, 2019) [30, 27].

Anti-hyperglycemic property

Diabetes mellitus (DM) is a chronic metabolic condition characterized by hyperglycemia and abnormalities in carbohydrate, protein, and lipid metabolism (Rodrigues *et al*., 2019) [45]. Morus species are known for the treatment and prevention of diabetes due to their hypoglycemic activity, which raises AMPK (adenosine monophosphate-activated protein kinase) and GLUT 4 (glucose transporter protein 4) levels in the plasma membrane (Choi *et al*., 2016) [10]. Mulberry fruit polysaccharides (MFPs) have been shown in studies to dramatically reduce glycosylated serum protein (GSP) and fasting blood glucose (FBG) levels in hyperglycemic rats. It was discovered that MEPs can increase the level of insulin, which enhances the cells' insulin sensitivity (Chen *et al*., 2017) [5].

Treatment with an ethanolic extract of Morus nigra resulted in lower levels of fasting and postprandial glycaemia, as well as enhanced oral glucose tolerance and decreased lipolysis and proteolysis in diabetic rats induced by aloxane (Júnior *et al*., 2017) [20]. Another study showed that diabetic rats fed with two different fractions of mulberry fruit polysaccharides (MFP50 and MFP90) for seven weeks had a significant decrease in fasting glucose, fasting serum insulin, triglyceride, and oral glucose tolerance test-area under the curve (Jiao *et al*. 2017) [19]. The anti-diabetic activity of mulberry anthocyanins was studied in rats. The findings of the study revealed a drop in fasting blood glucose, cholesterol, and triglyceride levels, as well as an increase in adiponectin levels. This suggests that mulberry fruits have antihyperglycemic and anti-hyperlipidemic properties (Yan *et al*., 2016) [61].

Anti-hyperlipidemic activity

Obesity is described as an excessive fat accumulation that poses health risks (Manzoor *et al*., 2022) [31]. Obesity has been associated to diabetes, hypercholesterolemia, hyperlipidemia, hepatic steatosis, and atherosclerosis, and a decrease in the quantity of sugar absorbed has an effect on body weight (Rahman and Islam, 2021) [41]. The effect of mulberry fruit intake on lipid profiles in hypercholesterolemic patients (aged 30- 60 years) was investigated. The levels of TC and LDL cholesterol were significantly lower compared to the control group, demonstrating that mulberry fruits could improve lipid profiles in hypercholesterolemic patients (Sirikanchanarod *et al*. 2016) [50].

Anthocyanin extracts from mulberries inhibited fat buildup caused by oleic acid. Triglyceride synthesis-related proteins and cholesterol biosynthesis-related proteins were decreased, whereas free fatty acid-related proteins were increased, showing that mulberry fruit anthocyanin extracts regulated lipid biosynthesis and lipolysis to produce hypolipidemic effects (Li *et al*., 2020) [26]. There was additional evidence that moracin C in mulberry fruit inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) mRNA transcription and hence decreases LDL receptor degradation, thereby lowering cholesterol levels (Pel *et al*., 2017) [39].

Anti-inflammatory activity

Mulberry plants have a long history of being used as anti-inflammatory medicines in traditional medicine. Numerous researches have shown that black mulberry is high in polyphenols, flavonoids, and anthocyanins, which are responsible for anti-inflammatory activity (Chen *et al*. 2016) [6]. Anthocyanin found in the fruits of *Morus nigra*, has been shown to have anti-inflammatory properties by reducing pro-inflammatory cytokine production in mice (Acharya *et al*., 2022) [1]. Cyanidin-3-glucoside (C3 G) is an anthocyanin found in mulberry fruits that is responsible for altering many hematological parameters in animal systems, including reducing inflammatory response blood triglycerides, and high-density lipoprotein cholesterol (Ramappa *et al*., 2020)

[43].

Extracts of *Morus nigra* pulps and leaves improved survival rates and reduced the number of total leukocytes in bronchoalveloar lavage fluid in lipopolysaccharide (LPS)-induced septic mice, showing a reduction in inflammatory infiltration in the lungs (de Pádua Lúcio *et al*., 2018) [11]. Flavonoids and other similar chemicals extracted from *Morus alba* had anti-inflammatory properties. Mulberry has been shown to inhibit the secretion of nitric oxide (NO), prostaglandin E2 (PGE2), other inflammatory factors, and the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in a dose-dependent manner, which may be related to the high resveratrol content in mulberry (Zhu *et al*., 2017) [67].

Anti-cancer activity

Cancer is a major public health issue all over the world. Clinically, the mulberry plant can inhibit cell proliferation, most likely due to the presence of flavonoids, which are particularly effective against some types of cancer (Jan *et al*., 2021) [17]. Many naturally occurring compounds have anti-cancer effects through tumor cell apoptosis and cell cycle arrest, which is regarded to be the best strategy to avoid abnormal cell growth (Dewanjee *et al*., 2017) [13]. The medicinal value of the mulberry plant has been known to people from the beginning of time. *Morus nigra* fruits, leaves, and bark antioxidant compounds have been demonstrated to have anticancer effects in addition to other benefits (Memete *et al*., 2022) [32].

Anthocyanins contained in *M. nigra* fruits, such as cyanidin and pelarginidine, have been shown to inhibit cancer cell viability and suppress tumour development (Khalifa *et al*., 2018) [21]. Mulberry fruit hydroxynamic acid derivatives have been demonstrated to promote reactive oxygen species generation by acting as prooxidants, thereby damaging cancer cells (Cho *et al*., 2017) [9]. The phenolic component of MFE ethyl acetate extract inhibited tumor growth by 70-80% with S-phase cell cycle arrest (Alam *et al*., 2016) [2].

Effect of different preservation methods on phytochemical profile of mulberry fruits

Drying

Drying is the process of removing water from solid and liquid goods using heat, resulting in solid-dried products (Calín-Sánchez *et al*., 2020) [4]. Mulberry fruit has a high moisture level, hence it is considered highly perishable. This fruit is dried for consumption as dried fruit or further usage in industrial products because to its strong potential uses in food and pharmaceutical applications (Ali *et al*., 2016) [3]. Fresh mulberry fruits are dried in the open air and consumed during the extreme winter season in Asian nations such as Pakistan, Turkey, Iran, and Uzbekistan. This approach is very ancient and unhygienic, uncontrolled, and not resistant to bacteria and pests (Khattak *et al*., 2019) [22]. Drying has become more sophiscated and complex in recent years due to the extensive use of technology and thorough examination and optimization of drying parameters at each stage of the process (Kozlowska *et al*., 2021).

More antioxidants were retained in mulberries dried using a solar air heater, followed by microwave drying, and the least in open sun drying. Drying techniques have evolved from traditional natural drying and hot air drying to modern vacuum drying (VD) and vacuum freeze-drying (VFD) (Tan *et al*., 2021) [53]. VD decreases oxidative damage due to the scarcity of oxygen, although it is time-consuming. The VFD technique involves sublimating water from a frozen matrix, which efficiently preserves the majority of the phytochemical features of fresh fruits (Papoutsis *et al*., 2017) [36]. The best approach for preserving phenolics, flavonoids, and antioxidants is hot air drying mulberries at temperatures below 50 °C. The amount of antioxidants retained in dried mulberries was only affected by the drying process, with no significant effects of preservatives or species on antioxidant retention (Khattak *et al*., 2019) [22].

Freeze-drying

It is generally accepted that the storage and processing conditions have a significant impact on the amount of biological phytochemicals; mainly carotenoids, phenolic antioxidants, and vitamin C in fruits and vegetables (Sultana *et al*., 2011) [51]. In terms of functional quality retention, freeze-drying is one of the most recommended procedures. Freeze drying involves freezing the water from the raw material and heating the frozen solid to induce moisture sublimation (Rahman, 2020; Szychowski *et al*., 2018) [42, 52].

Numerous studies also demonstrate that freeze-drying effectively preserves natural color (i.e. black mulberry). It inhibits microbiological deterioration, oxidation, and increases food shelf life. Freeze-drying improves the antioxidant potential and total phenolic content of *Morus nigra* when compared to fresh fruits (Calín-Sánchez *et al*., 2020) [4]. Another benefit of this technique is that there is no noticeable loss of flavor or aroma. Black mulberry dried with freeze drying followed by explosion puffing drying, an intermediate drying method, was shown to have the best color and hence maintain the highest anthocyanin content (Chen *et al*., 2017) [6].

Freezing

Fresh fruit has a very limited shelf life, so either it is processed right away or frozen (especially black mulberries) for later use. Freezing is a popular long-term preservation strategy for fruits, as it retains freshness properties far better than other conventional preservation methods such as sterilizing and drying (van der Sman, 2020) [58]. Frozen fruits preserve their physical structure, nutritional value, and sensory attributes. Frozen fruit pulps are a valuable source of raw material and bioactive components, and they are widely used in the food industry to make various fruit-based products (Orqueda *et al*., 2021) [35]. The levels of antioxidants can be efficiently stabilized by cool storage, which delays the activation of the oxidases (Zhao *et al*., 2017) [66].

Frozen storage (-25 ℃) had a substantial effect on the concentration of phenolic acids in both black and white mulberry fruits. The phenolic acid contents in frozen fruit were lower as compared to fresh fruits. The content of chlorogenic acid in both black and white mulberry fruit also fell considerably during the first three months of frozen storage (Pérez-Lamela *et al*., 2021) [40]. The number of certain flavonoids in black and white mulberry fruits at frozen storage (25 ℃) was determined. The levels of black mulberry were dramatically reduced after frozen storage; however, no significant changes were detected for white mulberry (Pehluvan *et al*. 2015) [38]. Regardless of storage duration, frozen storage resulted in considerable decreases in rutin content in black mulberries.

Conclusion

Mulberry is one of the most studied plants in terms of pharmacological potential. Over the years, research has revealed the presence of a number of active components in it. The current study focuses on antioxidants, polyphenols, and other phytochemicals that have anti-cancer, anti-inflammatory, anti-obesity, hypolipidemic, anti-diabetic, anti-microbial properties. The study also shows the effect of preservation methods on anthocyanins, phenols, and other phytochemicals. As mulberry fruits are only available in fresh form for a short time, thus they are best stored at low temperatures, occasionally dried, and processed into various goods to keep optimum nutrient content. The most extensively utilized physical methods of fruit preservation are based on temperature-related processes. Drying, VD, VFD, and freezing are some of the methods used to preserve mulberry fruits. All techniques have advantages and disadvantages, but the most important for a technique is to reduce cost, be eco-friendly, and ensure high quality dried products from a functional, physical, and sensory viewpoint.

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