Health benefits of Mulberry fruit extract: a review

Darathi Khound[1] ; Papori Borah [2]
Email id: darathiborah6@gmail.com
Project Associate-I; CSIR-NEIST, JORHAT-Assam.

Abstract

Since ancient times, a variety of plants have been used to treat various human diseases or to alleviate illnesses in traditional ways. Over time, these effects have been scientifically studied and published among people by different researchers. Mulberry fruit is one of these medicinal fruits that can treat a number of human diseases. The bioactive and aromatic compounds of the fruit have a number of health benefits at physiological and molecular level.

Keywords: Mulberry, extract, health, diseases.

INTRODUCTION

Mulberry is a large, deciduous, fast growing plant belonging to the family Moraceae and genus Morus. The term 'Morus' came from latin word *'mora'* which means delay and it is probably because of very slow development of its buds. Mulberry trees were first reported in China and also cultivated by Chinese people for the first time. The mulberry fruit was designated as one of the first medicinal-and-edible plants by the Ministry of Health of China in 1985. They are used to feed silkworms for the silk industries, making them a valuable commodity economically and the tree grows as fast as the silkworm larvae eat them. But, more than just a food, the germ-plasm of the tree was brought to different countries around the World and now it is widely distributed from Korea to Spain, India, Central and East Asia, North and East Africa, from the United States to Argentina, including Mexico, Central America, Colombia and Brazil.Most parts of mulberry plants are used as medicine in Chinese and Indian medicine *(Yang X, et al. 2010)*. There are mainly 3 species of mulberry which can be distinguished and identified by their bark, leaf shape and fruit color which are **Black Mulberry,(*Morus nigra)* Red Mulberry(*Morus rubra)* and White Mulberry (*Morus alba).***

Black Mulberry (***Morus nigra***), grow up in East, West and South-East Asia, South Europe, South of North America, Northwest of South America and some areas of Africa *(Calín-Sánchez et al. 2013)* and also in Turkey. It is a deciduous, medium-sized, fast-growing tree with heart-shaped which grows upto 12 m (39 ft) tall and 15 m (49 ft) broad. It has 308 chromosomes. The edible fruit of Mulberry is large , fleshy,

delicious, juicy, sweet-tart flavoured, dark purple in colour, which turns almost black when ripe and have laxative, odontalgic, antihelmintic, expectorant, hypoglycemic and antimicrobial effects. *(Mandal and Kumar 2002, Kone et al. 2004, Lin and Tang 2007, Ozgen et al. 2009).* The long and narrow edible fruits of ***Morus nigra*** are green in color when young which turns orange to red and finally to purplish black when fully ripened, which is considered as their most defining characteristic with a very sweet flavor. Due to high content of phenolic compounds including flavonoids, anthocyanins, phenolic acids and carotenoids it is considered as the healthiest fruit among mulberry species. Anthocyanins specially **cyanidin-3-glucoside** and **cyanidin-3-rutinoside** has been reported as the most powerful bioactive components of black mulberry as compared to other mulberry fruits and some other bioactive compounds isolated from this plant having analgesic and anti-inflammatory effects are used as herbal medicines for treatment of animals and humans.

White Mulberry ***(Morus alba)*** is distributed across North America and all of the United States with exception of Nevada and Canada. In Canada, it is found in British Columbia, Ontario and Quebec. It is a dense, perennial shrub, reaching height of about 50 feet having simple, ovate and alternate leaves of about 2-4 inches long and 1-2 inches wide. Fruits are cylindrical drupes about 0.5 to 1.0 inches long. Five main beneficial compounds viz. **butyl pyroglutamate, quercetin 3-*O*-β-d-glucoside, kaempferol 3-*O*-β-d-rutinoside, rutin, and 2-phenylethyl d-rutinoside** has been isolated of which **butyl pyroglutamate** possess protective effect against cisplastin-induced kidney cell damage. Total phenolic content is 104.78 to 213.53 mg GAE/100g DW and total flavonoid content is about 69.58 TO 211.01 MG ce/100 g DW. Major flavonoid compounds were **cathecin, procyanidin, quercetin, rutin** and **epicathechin**, while **gallicacid,cinnamic acid, p-hydroxybenzoic acid** were found as major phenolic acids.

Red Mulberry ***(Morus rubra)*** is native to eastern and central North America which is widely distributed in India, China, Japan, North Africa, Arabia, and southern Europe and globally distributed in different climatic conditions, ranging from tropical to temperate. It is an endangered species in Canada. ***Morus rubra***, or **Red Mulberry**, have short trunk, wide spreading branches and is a fast growing species which can reach up to 20 meters in height having dark grey-brown coloured bark with horizontal lenticels with yellow or green colored flowers. Its leaves are 5.0−7.5 cm in length, tear drop shaped, rough in texture, glossy green in color, alternate and acuminate at the apex with long and slender petioles.

Red mulberry ***(Morus rubra)*** fruit is rich in anthocyanin and the ascorbic acid content were determined as 124.5 g g−1 fw but the lipid content is 4.24% which is lower in comparison to ***M. nigra*** and ***M. alba*.** The

fatty acid (FA) profile is mostly linoleic for all species, followed by palmitic acid.

Bioactive and Aromatic compounds of the fruit extract

Flavonoids: Flavonoids are a group of plant metabolites found in deeply colored fruits, vegetables and different plant products. Major flavonoids in mulberry leaf include **isoquercitrin, astragalin, kaempferol, quercetin, and rutin** . Flavonoids derived from mulberry are useful in improving animal performance and health and can mediate the transcriptional signaling of different genes related to fat metabolism. Using HPLC-DAD-ESI-MS/MS method , six non anthocyanin phenolics were identified (***procatechuic acid, chlorogenic acid, 4-caffeoylquinic acid, taxifolin, rutin, quercetin***) and three others (***3,5-diCQA, taxifolin-hexoside, kaempferol-hexoside***) were tentatively identified.

Anthocyanin: Anthocyanin are a type of flavonoid, a family of powerful antioxidants that are of great interest as alternatives to synthetic colourants which are responsible for different colors like blue, red and purple of leaves, flowers and fruits and are of health benefits. Due to the presence of this phenolic compound in mulberry fruit; it exhibits a variety of biological activities such as **anti-thrombotic**,*(Yamamoto et al;2006),* **antioxidant** *(Kim et al;1999; Naderi, Asgary, Sarraf-Zadegan, Oroojy & Afshin-Nia,2004),* **antimicrobial** *(Takasugi, Nagao,Masamune, Shirata & Takahashi,1979)* anti inflammation *(Kim & Park 2006)* & **neuroprotective effects** *(Kang, Hu r, Kim & Ryu & Kim,2006)* and also for curing other health issues such as **dizziness**, **blurred vision, cardiovascular diseases, cancers, anti-inflammatory and chemoprotectiveproperties** *(Tsuda et al., 1994, 1998; Meiers et al., 2001; Bagchi et al., 2004; Lazze et al., 2004)*. The anthocyanin present in mulberry are **cyanidin-3-glucoside** and **cyanidin-3-rutinoside** *(SuhH.J.et al; 2003).* **Cyanidin-3- glucoside** ranges from 147.68 to 2725.46mg/L juice. Anthocyanins **cyanidin 3-O-rutinoside (60%)** and **cyanidin 3-O-glucoside (38%)** are found abundantly in mulberry pigment whereas **pelargonidin 3-Oglucoside** and **pelargonidin 3-O-rutinoside** are present in very less amount which is almost 2%.

Polysaccharides : Polysaccharides are complex bio macromolecules that are made up of chain of monosaccharides. Polysaccharides present in mulberry fruit has strong antioxidant, antidiabetic, hepatoprotective, prebiotic immunomodulatory , antitumor and antimicrobialproperties. *(Ai Jian et.al.2021, Jiao Y.et. al.,2017)*.

Phenols : Phenol (also called carbolic acid) is an aromatic organic compound. Phenolic acids extracted from mulberry fruit are mainly present as **benzoic acid** and h**ydroxycinnamicacid**. (*Mahmood*

et al.(19) revealed that mulberry fruit contain chlorogenic acid as most teeming phenolic acid derivative, while *Butkhup, Samappito, and Samappito* quantified that cinnamic acid was the most abundant phenolic acid derivative extracted from the mulberry fruit. Mulberries also contain quinic acid, which may help to alleviate urinary tract infection

Ethanol : The ethanol extract of mulberry leaves are well known to have multiple bioactivity including antimicrobial, antioxidant, and α-amylase inhibition activity.

Odisolane and antiangiogenic constituents: A compound known as odisalone or tetrahydro-2-hydroxy-2-methylfuran-3-propanoic acid identified in mulberry fruit exerts an anti-angiogenesis effect for cancer treatment by suppressing the protein expression of VEGF, p-Akt, and p-ERK.

Health benefits of compounds extracted from mulberry fruits on physiological and molecular level

• It lowers the cholesterol level in the body

Mulberry fruit extract has the specific capacity of lowering serum high density lipoprotein cholesterol (HDL-C) levels. Mulberry fruit inhibits hepatic sterol-regulatory element binding protein (Srebp) 2 gene expression and upregulated hepatic mRNAlevels of liver X receptor alpha, ATP binding cassette transporter 5 (Abcg5) and cholesterol 7-alpha hydroxylase (Cyp7a1) which are involved in hepatic bile acid synthesis and cholesterol metabolism.

• Prevents constipation

Mulberry fruit extract has remarkable therapeutic effects. A study on diphenoxylate induced constipation in mice, it was observed that mulberry fruit extract can increase the gastric-intestinal transit rate by increasing faecal water content. It increases the concentrations of acetic, propionic, butyric, valeric and isovaleric acid and also the abundance of lactobacillus and Bifidobacterium in faeces.

• Improves postmenopausal metabolic syndrome

Women faces a number of postmenopausal endocrine-metabolic syndrome such as hyperglycemia, dyslipidemia, hypertension etc. Encapsulated mulberry fruit extract improves metabolic syndrome during postmenopausal period which was also proved after several experimentations in female wistar rats. The extract improved weight gain, glucose intolerance, adiposity index, lipid profiles, atherogenic index, ACE, oxidative stress status, and protein expression of TNF-α and NF-κB.

• Lowers serum alcohol and acetaldehyde levels

Water and ethanol extract of mulberry can reduce acute alcohol-induced hangover and liver and brain damage by lowering serum alcohol and acetaldehyde levels.

• Improves memory power

Phytochemical compounds present in Mulberrry fruit extract improves oxidative status and enhanced

the the densities of neuron in CA3 and cholinergic neuron in Hippocampus. These can give rise to increased encoding ,retrieval capacity and memory power. Moreover, a flavonoidpigment known as anthocyanin in mulberry fruit could protect against cerebral ischemia.Mulberryfruit extract has cognitive enhancement capacity and is a neuroprotectant. It can decrease oxidative stress and apoptosis.

• Ameliorates adipogenesis.

Morus alba fruit extract decreased lipid and triglyceride accumulation and glycerol-3-phosphate dehydrogenase activity . In addition to this, mRNAgenes and microRNA—miR-21 and miR-143 responsible for adipogenesis are suppressed by mulberry fruit extract.

• Anti inflammatory activity of black mulberry in sepsis

Sepsis is an organ dysfunction which results from dysregulated response of the host to infection. It leads to irregular inflammation of cell due to overproduction of cytokines. Inflammatory cells can produce more reactive species which can enhanced redox reactions in the body. However, due to the presence of polyphenols, flavonoids, and anthocyanins in mulberry, it has the capacity of reducing redox reaction and number of inflammatory cells in bronchoalveolar lavage with therapeutic potential to minimize damage.However, serum level of TNF,GPx (Glutathione peroxide) and MMP2 (Mellalo proteinase) activities get decreased and restoration of GSH (glutathione)level takes place. Anti inflammatory activity of one flavonoid i.e; Delphinidin was well reported.

• Anti inflammatory and antioxidant activities of black mulberry

The secondary metabolite named 'flavonoids' present in black mulberry is associated with anti inflammatory and antioxidant activities . In sepsis pathogenesis, consequent production of inflammatory mediators and reactive species takes place. However, on treatment with *Morusalba,* these consequences related to sepsis can be cured.

• Reduce blood pressure

Ethanolic extract of mulberry fruit extract has beneficial effect on vascular remodelling and produces hypotensive effects through the eNOS signalling pathway. This extract has effects on smooth muscle proliferation and vascular contractility.

• Alleviates cognitive impairment and beta amyloid toxicity in neuronal cells of Alzheimer patient

In Alzheimer patient,Amyloid β peptide deposition leads to synaptic degeneration and interacts with different types of CNS receptors disrupting the process of neuronal homeostasis. *Lyengarin 2007* suggested that mulberry extract provide viable treatment to Alzheimer's disease through inhibition of amyloid beta- peptide (1-42) fibril formation and attenuation of neurotoxicity induced by amyloid beta- peptide

• Anti diabetic activities

Phytochemical analysis of the ethanolic extract of *Morus alba* led to isolation of 2 main compounds- rutin and quercetin-3-O-β-D glucoside which can

improve glucose uptake via Aktmediated insulin signalling pathway or AMP activated protein kinase activity in 3T3-L1 adipocytes tissue. Mulberries also contain the compound 1-deoxynojirimycin (DNJ), which inhibits an enzyme in your gut that breaks down carbs. Therefore, mulberries may be beneficial against diabetes by slowing down the increase in blood sugar after meals. Studies in people are needed before any firm conclusions can be reached.

• **Alleviates streptozotocin induced diabetic nephropathy**

Black mulberry fruit extract downregulates TNF-α, VCAM-1 and fibronectin mRNA expression in renal tissues of diabetic rats. Thus it improves diabetic nephropathy. (Include aboot diabetic nephropathy).

• **Protection against hepatocyte lipotoxicity**

Palmitic acid is a most abundant free fatty acid which has the ability to increase levels of cholesterol and promote fat deposition in coronary arteries. This leads to lipotoxiocity in the organs of human body and elevates the number of Reactive Oxygen Species.(ROS).Polysaccharide fractions of mulberry fruit extract has protective effects against palmitic acid induced hepato cyte lipotoxicity lipotoxicity through Nrf2/ARE signalling pathway as polysaccharide fraction has strong antioxidant activity.

• **Protection against ethyl carbamate induced cytotoxicity and oxidative stress**

Ethyl carbamate is found in various fermented products which has the potential of cytotoxicityand genotoxicity. These toxicity associate with accumulation of Reactive Oxygen Species.Presence of phenolic acids, flavonoids and anthocyanin. Mulberry fruit extract has protective action against Ethyl Carbamate (food and environmental toxicant) induced cytotoxicity and oxidative stress by protecting Caco2 cells from oxidative damage.

• **Effects on hypotensive activities**

Ethanolic extract of mulberry fruit prevents smooth muscle proliferation, thickening of the tunica media and vascular hyperreactivity a nd thereby normalizes hypertension.

• **Enhancement of antioxidant activity**

Morus alba fruit extract protects insulin producing pancreatic β cells against hydrogen peroxide induced oxidative stress and associated apoptotic cell death.

• **Prevents alcohol induced steatosis**

Consumption of alcohol causes hepatic steatosis or fatty liver which mainly takes place due to high levels of fat especially triglyceride in our blood and as a result large vacuoles of triglyceride fat accumulates in the liver cells. As liver plays a vital role in storage of glycogen; therefore glucose level in the blood also increases. Water extract of mulberry helps in ethanol degradation and prevents hepatic steatosis due to alcohol intake. In addition to this, the extract also ameliorate gut microbial imbalance h due to consumption of alcohol.

• **Protective effect in testosterone induced benign prostatic hyperplasis**

Black mulberry extract has protective effect against experimentally induced BPH or Benign Prostatic Hyperplasia.

• Protection against cerebral ischemia

A steady supply of oxygenated blood supply is required to maintain proper brain health and function. Cerebral ischemia is a type of stroke which occurs due to interruption in blood supply to the brain. Cyanidin-3-0-beta-d-glucopyranoside extracted from mulberry fruit haveneuroprotective effects. The extract inhibited cerebral ischemic damage caused by glucose deprivation in PC12 cells.

• Ameliorates Parkinson disease related pathology

PD is a dopaminergic neuronal disorder that affects the movement of human body. Mulberry extract regulates the mechanism of upregulation of excitatory neuronal proteins anddownregulation of inhibitory neuronal protein. It alleviates the dopaminergic neuronal degeneration via antioxidant and antiapoptopic effects.

• Derivatives against human cervical cancer

2 Indole acetic derivatives from mulberry fruit has been proved to have cytotoxic effect on human cervical cancer hela cells. The compound activates the whole caspase pathway.

• Anti- fatigue effects

Flavonol, phenolic and anthocyanin content of mulberry has the antifatigue activities. (Jiang et al.,2013)

• Prevents hepatocarcinogenesis

Hepatocellular carcinoma is the most common malignancies case. Rats treated with diethylnitrosamine (a chemical which can induce hepatic tumurogenesis) were injected with mulberry polyphenol extract (MPE) and mulberry water extract (MWE) and it was observed that these extract can reduce the rate of tumurogenesis as well as MPE can reduce the growth of HepG2 and Hep3B cells.

• Atherosclerosis

Ethanol extract of black mulberry can enhanced anti oxidative properties which can reduce abnormalities in lipid metabolism; thereby inhibiting atherosclerosis. This extract also downregulates atherosclerosis related inflammatory factors.

• Protection against haemolysis

An anthocyanin compound present in mulberry fruit known as cyanidin-3-O-glucoside has been proved to possess protective effects on mouse red blood cell haemolysis.

• Antiallergic actions

In combination with naringinase Mulberry fruit extract perform anti-allergic actions in IgEactivated RBL-2H3 cells. It enhanced the inhibitory effects of MFE on the release of β-hexosaminidase and TNF-α. Has inhibitory effects on allergic response through the suppression of FceRI signalling cascade.

• Protection against benzo pyrene induced skin damage

A Polycyclic aromatic hydrocarbon - benzopyrene is a procarcinogen. Extract of mulberry fruit has protective effect against benzopyrene induced cytotoxicity ag ainst human keratinocytes.Pretreatment with

the extract repress the AhR signalling pathway.

• Lavodopa induced dyskinesia

As blackberry is rich in anthocyanin which is a strong antioxidant, it is important in the treatment of neurodegenerative diseases such as lavodopa induced dyskinesia in Parkinson's disease.

• Anxiolytic, hypnotic and sedative effects

Morinda fruit extract is considered as a supplement in patient with anxiety disorders because the extract ha high binding affinity to the Gamma-aminobutyric acid receptors as neu rohormonal system GABA is responsible for mediation of all anxiety related issues.

• Delay aging

Mulberry leaf polyphenols having high oxidative activity could delay aging using the short-lived nematode *C.elegans.*

•Hepatoxic effect

In a lifespan of human, our liver can be affected by various hepatotoxic chemicals such as CCl4 c and drugs like paracetamol, etc. Here, different parts of Mulberry plays an important role. The extract also decreased lipid peroxidation and helps in preventing aspartate aminotransferase(AST) and gamma-glutamyl transferase, resulting in the improvement of histological appearance of the liver. Among *M. nigra* anthocyanins, cyanidin-3-glucoside, delphinidin, and pelargonidinplays a major role in the hepatoprotective properties of this plant.

• Antithrombotic effect

Morus alba L. contains an active yellow crystalline flavonol which is known as **Morin hydrate**,Which induced human platelet aggregation by acting on collagen and thrombin thus can be consumed by thrombotic patient for their treatment.

• Antioxidant activity

Morus alba possesses antioxidant activity, which provides protection against free radicals. Studies have found that mulberry provides protection against chemically-induced carcinogens by boosting antioxidant levels. Mulberry fruit polysaccharide exhibit potent antioxidant activity in vitro, because it scavenge DPPH, hydroxyl and oxygen radical and prevent H_2O_2 induced oxidation.(Wang,Wei et al; 2018)

• Antimicrobial activity

As mulberry extracts are rich in phytochemicals, they have antimicrobial properties against harmful pathogens. Leaf extract of Mulberry is best against bacterial and fungal cultures. The ethanolic extract of mulberry **(*Morus indica*)** is potent against four dental caries-causing bacterial strains viz. ***Streptococcus mutans***, ***Escherichia coli*** (***E. coli***), ***Staphylococcus aureus (S. aureus)***, and ***Bacillus subtilis (B. subtilis***). The fresh juice extract derived from mulberry fruit shows antibacterial activity against the Gram-positive and Gram-negative bacteria. Kuwanon G (purified from methanolic extract of *M. alba*), moracin, morusin, isolated from wood and stem bark of *M. nigra* have antimicrobial property.

• Gastroprotective value

The fruit extract of *Morus alba* has gastroprotective value too.

By concentrating the methanolic compound extracted from the fruit on phenolics, their oxidative value decreases and as a result helps to fight against gastric.

• Penicillin induced epileptiform induced activity

Penicillin drug cause seizures and jerky movements. Mulberry extract decreases the level
of genotoxic product; malondialdehyde level s both in erythrocytes and plasma which reduces the thesaurus of epilepsy.

• Chemotherapeutic activity

Several natural phytochemicals have the capacity of activating the immune cells such as T-lymphocytes, Natural Killer cells etc. Which can boost the antitumour activity in the body. The extract of *Morus alba* fruit is helpful in the treatment of cancer by immune system enhancement through activation of cytokines and immune cells.

CONCLUSION AND FUTURE PROSPECTIVES

For more than 5000 years, mulberry plant has been recognized all over the world as a food for silkworm ***(Bombyx mori)*** and has been widely used as a traditional medicine for a long time due to its pharmacological properties. This plant is a rich source of flavonoids. But, now it is used in many diverse fields as it is considered as a multipurpose plant by utilizing in environmental safety approach, promotion of human health and in promoting animal husbandry through quality milk production and enhanced meat production and its leaf is traditionally consumed as a functional tea with remedial effects, such as preventing aging-related diseases and have a variety of culinary, medicinal, and industrial applications.

Further studies are required on some unidentified biological compounds of mulberry which require proper exploration and identification of the mechanisms and pathway for ROS production and scavenging in the mulberry chloroplast. Deep comparison of the difference between the covalent and non covalent interactions on the protein's digestibility, as well as the underlying mechanisms are needed in the future.

Besides these, structural and functional genomic analysis of Mulberry genome as well as detailed study of the compounds extracted from these berries must implement the compounds in different beneficial fields. Commercialization of Mulberry products is an important and finalized part of all these study so that people can understand and extract benefits from these products.

REFERENCES

Abouzed TK. "Black mulberry fruit extract alleviates streptozotocin-induced diabetic nephropathy in rats: targeting TNF-α inflammatory pathway." *Journal of Pharmacy and Pharmacology* 2020; 72(11): 1615-1628

Ai J, Bao B, Battino M, Giampieri F, Chen C, You L, Acuna CL, Ognyanov M, Tian L & Bai W . "Recent advances on bioactive polysaccharides from mulberry." *Food & Function* 2021; 12(12) : 5219-5235.

Arabshahi D, Saeedeh, & Asna U. "Antioxidant properties of various solvent extracts of mulberry (Morus indica L.) leaves." *Food chemistry* 2007 ;102(4): 1233-1240.

Asano N, Oseki K, Tomioka E, Kizu H & Matsui K. "N-containing sugars from Morus alba and their glycosidase inhibitory activities." *Carbohydrate research* 1994 ;259(2): 243-255.

Bae SH & Suh HJ. "Antioxidant activities of five different mulberry cultivars in Korea." *LWT-Food Science and Technology* 2007 ; 40(6): 955-962.

Budiman A, Praditasari A, Rahayu D & Aulifa DL."Formulation of antioxidant gel from black mulberry fruit extract (Morusnigra L.)." *Journal of pharmacy & bioallied sciences* 2019;11(3): 216.

Burgess, KS, Morgan M, Deverno L & Husband BC. "Asymmetrical introgression between two Morus species (M. alba, M. rubra) that differ in abundance." *Molecular Ecology* 2005; 14(11): 3471-3483.

Luchai B ,Samappito W & Samappito S. "Phenolic composition and antioxidant activity of white mulberry (M orus alba L.) fruits." *International Journal of Food Science & Technology* 2013; 48(5): 934-940.

Sánchez AC, Nicolas JM, Picazo SM, Barrachina A, Legua P & Hernandez F. "Bioactive compounds and sensory quality of black and white mulberries grown in Spain." *Plant foods for human nutrition* 2013; 68(4): 370-377.

Chan, Chiang EW, Phui-Yan LE, & Siu-Kuin WG. "Phytochemistry, pharmacology, and clinical trials of Morus alba." *Chinese journal of natural medicines* 2016; 14(1): 17-30.

Chang BY, Kim SB, Lee MK,Park H & Kim SY. "Improved chemotherapeutic activity by Morus alba fruits through immune response of toll-like receptor 4." *International journal of molecular sciences* 2015; 16(10): 24139-24158.

Chen H, Pu J, Liu D & Yu W. "Anti-inflammatory and antinociceptive properties of flavonoids from the fruits of black mulberry (Morus nigra L.)." *PloS one.*2016 11(4): e0153080.

Dat NT, Xuan Binh PT, Phuong Quynh LT, Minh CV, Huong HT, Lee JJ "Cytotoxic prenylated flavonoids from Moru s alba." *Fitoterapia* 2010; 81(8): 1224-1227.

Padua lucio KD, Rabelo AS, Araujo CM, Brandao GC, Bianco de Souza GH, Gomes da silva R, Soares de Souza DM, Talvani A, Bezerra FS, Calsavara AJC & Costa DC"Anti-inflammatory and antioxidant properties of black mulberry

(Morus nigra L.) in a model of LPS-induced sepsis." *Oxidative medicine and cellular longevity* 2018.

Du, Zhen Q, Zheng JF & Xu Y. "Composition of anthocyanin in mulberry and their antioxidant activity." *Journal of Food Composition and Analysis* 2008. 21(5): 390-395.

Ercisli S & Orhan E. "Chemical composition of white (Morus alba), red (Morusrubra) and black (Morus nigra) mulberry fruits." *Food chemistry* 2007. 103(4): 1380-1384.

Fahimi Z & Jahromy MH. "Effects of blackberry (Morus nigra) fruit juice on levodopa-induced dyskinesia in a mice model of Parkinson's disease." *Journal of experimental pharmacology* 2018. 10: 29.

Ghorbani A and Hooshmand S. "Protective Effects of Morus nigra and Its Phytochemicals against Hepatotoxicity: A Review of Preclinical Studies." *Pharmacology* 2021;1-11.

Gundogdu M, Muradoglu F, Gazioglu Sensoy RI & Yilmaz H. "Determination of fruit chemical properties of Morus nigra L., Morus alba L. and Morus rubra L. by HPLC." *Scientia horticulturae* 2011; 132 : 37-41.

Ghazaleh H, Fazaeli M & Emam-Djome Z.. "Effects of heating method and conditions on the quality attributes of black mulberry (Morus nigra) juice concentrate." *International Journal of Food Science & Technology* 2011; 46(5): 956-962.

Hu D, Bao T, Lu Y, Su H, ke H & chen W. "Polysaccharide from Mulberry Fruit (Morus alba L.) Protects against palmitic-acid-induced hepatocyte lip otoxicity by activating the Nrf2/ARE signaling pathway." *Journal of agricultural and food chemistry* 2019; 68 (46): 13016-13024.

Hussain F, Rana Z, Shafique H & Malik A. "Phytopharmacological potential of different species of Morus alba and their bioactive phytochemicals: A review." *Asian Pacific journal of tropical biomedicine* 2017 ; 7(10): 950-956.

Isabelle M, Lee BL, Ong CN, Liu X & Huang D. "Peroxyl radical scavenging capacity, polyphenolics, and lipophilicantioxidant profiles of mulberry fruits cultivated in southern China." *Journal of agricultural and food chemistry* 2008; 56(20) : 9410-9416.

Kaewkaen P, Tong-un T, Wattanathorn J & Muchimapura S. "Mulberry fruit extract protects against memory impairment and hippocampal damage in animal model of vascular dementia." *Evidence-Based Complementary and Alternative Medicine* 2012 ?

Kamiloglu S, Serali O, Unal N & Capanoglu E. "Antioxidant activity and polyphenol composition of black mulberry

(Morus nigra L.) products." *Journal of Berry Research* 2013; 3(1): 41-51.

Kang TH, Hur JY, Kim HB, Ryu JH & Kim SY. "Neuroprotective effects of the cyanidin-3-O-β-d-glucopyranoside isolated from mulberry fruit against cerebral ischemia." *Neuroscience letters* 2006; 391 (3): 122-126.

Katsube T, Imawaka N, Kawano Y & Yamazaki Y. "Antioxidant flavonol glycosides in mulberry (Morus alba L.) leaves isolated based on LDL antioxidant activity." *Food chemistry* 2006; 97 (1): 25-31.

Kultu T, Durmaz G, Ates B, Yilmaz I & Cetin MS "Antioxidant properties of different extracts of black mulberry (Morusnigra L.)." *turkish Journal of Biology* 2011; 35 (1): 103-110.

Lee D, Yu JS, Lee SR, Hwang GS, Kang KS, Park JG, Kim HY & Yamabe N. "Beneficial effects of bioactive compounds in mulberry fruits against cisplatin-induced nephrotoxicity." *Int ernational journal of molecular sciences. 2018;* 19(4): 1117.

Lee MK & Kim Y. "Mulberry Fruit Extract Ameliorates Adipogenesis via Increasing AMPK Activity and Down regulating MicroRNA-21/143 in 3T3-L1 Adipocytes." *Journal of medicinal food* 2020; 23(3): 266-272.

Lee SR, Park JY, Yu JS, Lee SO, Ryu JY, Choi SZ, Kang KS, Yamabe N & Kim KH. "Odisolane, a novel oxolane derivative, and antiangiogenic constituents from the fruits of mulberry (Morus alba L.)." *Journal of agricultural and food chemistry* 2016; 64.(19): 3804-3809.

Lim HH, Lee SO, Kim SY, Yang SJ & Lim Y. "Anti-inflammatory and antiobesity effects of mulberry leaf and fruit extract on high fat diet-induced obesity." *Experimental Biology and Medicine* 2013 238.(10): 1160-1169.

Lim SH & Chang-Ik C. "Pharmacological properties of *Morus nigra* L.(black mulberry) as a promising nutraceutical resource." *Nutrients* 2019. 11 (2): 437.

Lin JY & Ching-Yin T. "Determination of total phenolic and flavonoid contents in selected fruits and vegetables, as well as their stimulatory effects on mouse splenocyteproliferation." *Food chemistry* 2007 ,101(1): 140-147.

Liu X, Xiao G, Chen W, Xu Y & Wu J."Quantification and purification of mulberry anthocyanins with macroporousres ins." *Journal of Biomedicine and Biotechnology* 2004.5 : 326.

Liu YG, Yan JL, Ji WJ & Jiang Y. "Black mulberry ethanol extract attenuates atherosclerosis-related inflammatory factors and downregulates PPARγ and CD36 genes in experimental atherosclerotic rats." *Food & function.2020.* 11.(4): 2997-3005.

Mahmoud HI, Gad EIRab SM, Khalil AF & Ismael SM. "Hypoglycemic effect of white (Morus alba L.) and black (Morus nigra L.) mulberry fruits in diabetic rat." *European Journal of Chemistry* 2014 5(1): 65-72.

Mandal SC & Ashok CK. "Studies on anti-diarrhoeal activity of Ficus hispida leaf extract in rats." *Fitoterapia* 2002; 73(7-8): 663-667.

Monson, Clark S. "Mulberry trees: the basis and remnant of the Utah silk industry." *Economic botany* 1996; 50(1): 130-138.

Naderi GA, Asgary S, Zadegan NS, Oroojy H & Afshin-Nia F. "Antioxidant activity of three extracts of Morus nigra." *PhytotherapyResearch: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 2004; 18(5): 365-369.

Nam GS, Lee KS & Nam KS. "Morin hydrate inhibits platelet activation and clot retraction by regulating integrin αIIbβ3, TXA2, and cAMP levels." *European journal of pharmacology* 2019;865 : 172734.

Natić MM, Dabic DC, Papetti P, Aksic MMF, Ognjanov V, Ljubojevic M & Tesic ZL "Analysis and characterisation of phytochemicals in mulberry (*Morus alba* L.) fruits grown in Vojvodina, North Serbia." *Food chemistry* 2015 171 : 128-136.

Naz S. "Determination of Antimicrobial Activity of Mulberry Fruit Extracts against Water-borne Microbial Pathogens Isolated from Different Water Samples." *University of Wah Journal of Science and Technology (UWJST)* (2018): 19-29.

Nesello LN, Beleza ML, Mariot M, Marilo LN, Souza PD, Campos A, Filho V,Andrade SF & De Silva LM. "Gastroprotective value of berries: Evidences from methanolic extracts of *Morus nigra* and Rubus niveus fruits." *Ga stro enterology research and practice* 2017.

Niratker C & Malti P. "Antimicrobial activity of leaf extract of *Morus indica* (Mulberry) from Chhattisgarh." *Asian Journal of Plant Sciences* . 2015; 28-31.

Mustafa O, Serçe S & Kaya C."Phytochemical and antioxidant properties of anthocyanin-rich Morus nigra and Morus rubra fruits." *Scientia Horticulturae* 119.3 (2009): 275-279.

Park SW, Shin KC, Yoou SK, Park HJ, Eun SH, Bae YM, Lee HM,Chae HJ, Chae SW & Choi BH. "Effects of an ethanolic extract of mulberry fruit on blood pressure and vascular remodeling in spontaneous hypertensive rats." *Clinical and Experimental Hypertension 2019;* 41(3): 280-286.

Pel P, Chae HS, Nhoek P, Kim YM & Chin YW.. "Chemical constituents with proprotein convertase subtilisin/kexin t ype 9 mRNA expression inhibitory activity

from dried immature Morus alba fruits." *Journal of agricultural and food chemistry* 2017; 65(26): 5316-5321.

Radojković M, Zekovic Z, Vidovic S & kocar D. "Free radical scavenging activity and total phenolic and flavonoidcontents of mulberry (Morus spp. L., Moraceae) extracts." *Hemijska industrija 2012;* 66(4): 547-552.

Rodrigues EL, Marcelino G, Silva GT, Figueiredo PS, Garcez WS, Corsino J, Guimaraes RA & Freitas KC "Nutraceutical and medicinal potential of the Morus species in metabolic dysfunctions." *International journal of molecular sciences 2019* ; 20(2): 301.

Stone KR. "Morus alba." *Fire Effects Information System,[Online]. US Department of Agriculture, Forest Service, Rocky Mountain Research Station, Fire Sciences Laboratory (Producer). Available:< http://www. fs. fed. us/database/feis/>. Accessed [9 April 2013]* (2009).

Wang Y, Xiang L, Wang C, Tang C & He X. "Antidiabetic and antioxidant effects and phytochemicals of mulberry fruit (Morus alba L.) polyphenol enhanced extract." *PloS one* 8.7 (2013): e71144.

Wattanathorn J, Supannika K & Wipawee T. "Encapsulated mulberry fruit extract alleviates changes in an animal model of menopause with metabolic syndrome." *Oxidative medicine and cellular longevity* 2019.

Yang HJ, Kim MJ, Kang ES, Kim DS & Park S. "Red mulberry fruit aqueous extract and silk proteins accelerate acute ethanol metabolism and promote the antioxidant enzyme systems in rats." *Molecular medicine reports* 18.1 (2018): 1197-1205.

Yang Y, Gong T, Liu C & Chen R. "Four new 2-arylbenzofuran derivatives from leaves of Morus alba L." *Chemical and Pharmaceutical Bulletin 2010* 58(2): 257-260.

Yang Y, Zhang T, Xiao L, Yang L & Chen R. "Two new chalcones from leaves of Morus alba L." *Fitoterapia* 2010 81(6): 614-616.

Yang X, Yang L & Zheng H. Hypolipidemic and antioxidant effects of mulberry (*Morus alba* L.) fruit in hyperlipidemia rats. Food Chem Toxicol, 2010; 48(8-9): 2374-2379

Yihai W, Liming X, Chunhua W, Chao T & Xiangjiu H. Antidiabetic and Antioxidant Effects and Phytochemicals of Mulberry Fruit (*Morus alba* L.) Polyphenol Enhanced Extract. Plos One Collection Antiviral innate immunity, 2013

Yilmaz S, Asli U & Bayram G. "Genotoxic and genoprotective potential of black mulberry (Morus nigra)

fruit." *Anais da Academia Brasileira de Ciên cias* 2019.

Yuan Q & Longyan Z. "The Mulberry (Morus alba L.) Fruit. A Review of Characteristic Components and Health Benefits." *Journal of Agricultural and Food Chemistry" 2017.* 65(48): 10383-10394.

Yuan Q, Lv K, Huang J, Sun S, Fang Z, Tan H, Li H, Chen D, Zhao L, Gao C & Liu Y. "Extraction optimization, characterization and antioxidant activity in vitro of polysaccharides from mulberry (Morus alba L.) leaves. " *Carbohydrate Polymers* 2015 128 : 52-62.

Zhishen J, Tang M & Wu J. "The determination of flavonoid contents in mulberry and their scavenging effects on superoxide radicals." *Food chemistry* 1999; 64(4): 555-559.