



E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2019; 8(1): 731-738
Received: 11-11-2018
Accepted: 16-12-2018

Iqra Rafiq

College of Temperate Sericulture,
Sher-e-Kashmir University of
Agricultural Sciences and
Technology of Kashmir Mirgund,
Jammu and Kashmir, India

ZI Buhroo

College of Temperate Sericulture,
Sher-e-Kashmir University of
Agricultural Sciences and
Technology of Kashmir Mirgund,
Jammu and Kashmir, India

Shahina A Nagoo

College of Temperate Sericulture,
Sher-e-Kashmir University of
Agricultural Sciences and
Technology of Kashmir Mirgund,
Jammu and Kashmir, India

Corresponding Author:**Iqra Rafiq**

College of Temperate Sericulture,
Sher-e-Kashmir University of
Agricultural Sciences and
Technology of Kashmir Mirgund,
Jammu and Kashmir, India

Mulberry (*Morus* spp.): A versatile tree with inherent bioactive compounds of promising pharmaceutical and nutraceutical properties

Iqra Rafiq, ZI Buhroo and Shahina A Nagoo

Abstract

Mulberry (*Morus* sp.) is one of the economically important trees grown in Asian countries. It is cultivated to provide leaves for feeding the caterpillars of the silk producing insect (*Bombyx mori* L.). It also adds value by producing edible fruits, wood, and a number of pharmaceutically essential chemicals. *Morus* has a diverse range of phytochemicals in its leaves, fruit, roots, and wood, which give it a diverse range of biological functions (Antioxidant, anti-diabetic, anti-obesity, anticancer, antibacterial, antiviral, crypto protective and neuroprotective activities etc.). Mulberry plants have attracted the interest of the pharmaceutical industry due to their lucrative health benefits. The primary objective of this review is to reveal the pharmacological mechanism and active principles found in mulberry plants, thus exposes the mulberry plant's wide range of life-saving pharmacological properties.

Keywords: mulberry (*Morus* spp), pharmaceutical and nutraceutical

Introduction

Mulberry, *Morus* spp. of the Moraceae family, is important in the sericulture industry because it is the primary food plant for the monophagous insect *Bombyx mori*. Mulberry is a fast-growing woody perennial plant with over 15 different deciduous varieties. The major ones include *M. alba*, *M. indica*, *M. nigra*, *M. rubra*, *M. australis*, *M. atropurpurea*, *M. cathayana*, *M. notabilis* and *M. mesozygia* [1]. Mulberry leaves have long been valued as a primary food source for silkworms, helping to sustain the silk industry. The silkworm eats only mulberry leaves to make its cocoon, produces silk, and there is a strong link between the leaf protein content and cocoon production quality [2]. Mulberry can be used as fodder for dairy animals because it is nutritious, palatable, non-toxic, and has the potential to increase milk production [3]. Mulberry leaves, fruits, and bark have been used to treat fever, protect liver damage, enhance eyesight, strengthen joints, promote urine discharge, and lower blood pressure [4]. *Morus* leaves, berries, root, and wood contain a broad variety of phytochemicals that have a wide range of biological functions (antioxidant, anti-diabetic, anti-obesity, anticancer, antibacterial, antiviral, cryptoprotective, and neuroprotective activities). Mulberry leaves are effective against high blood pressure and hangover from alcohol [2]. *M. alba* trees are cultivated for their fruits rather than their foliage in Turkey and Greece [5]. *M. alba* leaves are used to make tea in China, and fruit juice is consumed as a health beverage. Studies reveals that the nutritional composition of mulberry leaves on dry weight basis that it contains 15.31-30.91 per cent protein, 2.09- 7.92 per cent fat, 9.9-13.85 per cent crude fiber, 27.60- 43.6 per cent neutral dietary fiber (NDF) and 11.3-17.24 per cent ash contents [6]. Many scientists have studied the pharmaceutical properties of mulberry plants, and they have stated that many biochemical compounds isolated from mulberry plants, such as Moran line, Alba furan, Albanol, Morusin, Kuwanol, Calystegine, and Hydroxymorcin, play an important role in the pharmaceutical industry [7]. Also three flavonol glycosides, quercetin 3-(6 malonylglucoside), rutin, and isoquercitrin, have been reported as major antioxidant compounds in the ethanol leaf extract of *M. alba* [8]. Phytochemical studies of fruits of *M. alba* revealed that there are five anthocyanin's [9] and 25 phenolic compounds present in the fruit. From the root bark of *M. alba*, polyhydroxylated alkaloids have been isolated, including 1-deoxynojirimycin (DNJ) and its derivatives [10]. The nutritional potential and the huge popularity of the mulberry fruits motivated the investigations on the chemical con-tent and the antioxidant power of mulberry fruits find new promising sources of natural antioxidants.

Description

Mulberry is a small deciduous tree with a deep-root system growing to 10-13 m tall woody perennial plant. The leaves are 10-20 cm long and 6-10 cm wide (up to 23 cm long on robust shoots), downy on the underside, with very thin, stiff hairs on the upper surface rough and clear, alternate, stipulate, petiolate, whole or lobed leaves. Male catkins tend to be longer than those of female catkins. Male flowers are loosely spaced, and after pollen is shed, the inflorescence dries and falls off. The female inflorescence is typically small, and the flowers are arranged rather compactly. The calyx adheres to the ovary throughout the growth of the mulberry flower and is an accessory component of the drupelet. The fleshy bases of pollinated flowers begin to swell and eventually change their texture and color entirely, becoming succulent and full of juice. For certain species such as *M. alba* the fruits are white to pinkish and *M. rubra* is found to be red whereas *M. nigra* purple in color. Leaves in mulberry alternate, stipulate, variable in shape, lobed or unlobed, cordate, dentate, acuminate, long-petiolate, 12 x 8 cm on fruiting branches, up to 25 x 20 cm on vigorous non-fruiting branches, usually smooth above, glabrous or pubescent along veins beneath, thin, light green.

Diversity

Mulberry is considered to be originated in the border area of the Indo-Chinese region and distributed in the lower slopes of the sub-Himalayan zone up to an elevation of 3300 m [11]. Mulberries have, historically, been used in sericulture throughout the world including India. The major mulberry growing states in India includes states of Karnataka, Tamil Nadu, Kerala, Uttar Pradesh, Bihar, Madhya Pradesh, West Bengal, Rajasthan, Himachal Pradesh and Assam [12]. Huge diversity exists in available germplasm pool of mulberry in India. However, the breeding efforts on mulberries in India made so far were restricted to development of genotypes suitable for sericulture, which was primarily being carried out at Central Sericultural Germplasm Resources Centre, Hosur, Tamil Nadu. In India, mulberry is either grown as a field crop (plants kept in form of bushes and the leaves harvested several times a year for the multivoltine race of silkworms) or as a tree (leaves harvested only once a season for rearing univoltine races of silkworms). Japan has about 700 types of which 21 are extensively cultivated. Most important varieties grown in India is *M. alba* var. *multicaulis* Also, native of China, white mulberry is cultivated throughout the world wherever silkworms are raised, and is occasionally cultivated elsewhere in Europe, North America, and Africa. Having escaped, trees often appear on roadsides, along fencerows, and as ornamentals.

Mulberry cultivation is generally found in both tropical and temperate regions, although the temperature of 26 °C is ideal for cultivating mulberry. The average humidity should be between 70-90%. It grows well in areas where annual rainfall

varies between 600 and 2500 millimetres per hour with a minimum of 9.0 to 13.00 hours of sunshine per day. Mulberry can be grown up to 4000 meters above sea level [13]. The optimal soil pH range is 6.2-6.8. Because mulberry is a hardy crop, the soil moisture can be used to a greater extent by these plants [14].

Mulberry Nutrition

Plants contain a wide variety of bioactive molecules, making them a valuable source of various medicines. Over 50 per cent of all modern clinical drugs are of natural product origin [15] and natural products play an important role in drug development programs in the pharmaceutical industry [16]. Herbal drugs have gained importance in recent years because of their efficacy and low cost. Mulberry plant is one of conventional herbs which are used in medicine from centuries ago due to its chemical composition and pharmacological function. All most all parts of mulberry plants are used as medicine in Chinese and Indian medicine. According to a study it has been reported that mulberry leaves contain N-containing sugars, rutin, quercetin, volatile oil, amino acid, vitamins and microelements, which have so many pharmacological activities such as reducing blood glucose, antihyperlipidemia, hypertensive, bacteriostasis and antivirus [17]. Studies have reported many different medicinal properties of mulberry leaves [7, 18]. Pharmaceutical properties of mulberry plants are reviewed by [19]. They found that many biochemical compounds such as Moranoline, Albufuran, Albanol, Morusin, Kuwanol, Calystegin and Hydroxymoricin are isolated from mulberry plants which play an important role in pharmaceutical industry. Mulberry fruits have been reported to be 7.55% of all saturated lipids, with 87.5% of unsaturated FA such as the highest amount of linoleic acid (79.4%), followed by palmitic acid (8.6%) and oleic acid (7.5%) [34]. The content of the total lipids in Turkish mulberry fruits (57.3%) and Palmitic acid (22.4%). The poly unsaturated fatty acids content in mulberry fruit is more than mono unsaturated fatty acids and saturated fatty acids [20]. Linoleic acid, a predominant fatty acid, is present in mulberry fruit as an essential polyunsaturated fatty acid and plays a key role in human growth, health promotion, and disease prevention in human beings [21, 22]. The difference in the fruit colour vary due to the anthocyanin pigment content. Mulberries are a kind of berry that grows on trees. Because of the high moisture content, it is vulnerable to storage. The tartness of fruit comes from its acidity. Mulberries contain more malic acids than citric acids (Table 1). The most prevalent flavonoids are rutin, quercetin, and morin. Between the vitamins, mulberries contain adequate quantities of vitamin C as well as vitamins abundant in the B-complex such as vitamin B2, B3, B6, B9, Vitamin-E (tocopherol), and Vitamin-K (phyloquinone). Vitamins like these act as cofactors in the body's protein, and fat metabolism.

Table 1: Organic acid contents (g/100g of fresh weight) of mulberry

| Mulberry Genotypes | Citric acid | Malic acid | Tartaric acid | Acetic acid | Succinic acid | Lactic acid | Fumaric acid |
|---------------------------------------|-------------|------------|---------------|-------------|---------------|-------------|--------------|
| Black Mulberry (<i>Morus nigra</i>) | 1.084 | 1.323 | 0.123 | 0.019 | 0.342 | 0.049 | 0.011 |
| White Mulberry (<i>Morus alba</i>) | 0.393 | 3.095 | 0.223 | 0.008 | 0.168 | 0.074 | 0.024 |
| Red Mulberry (<i>Morus rubra</i>) | 0.762 | 4.467 | 0.336 | 0.015 | 0.132 | 0.074 | 0.02 |

(Source: Sánchez-Salcedo *et al.*, 2015)

Bioactive Compounds in Mulberry

• Flavanoids

The genus *Morus* is a rich source of flavanoids, and most flavanoids are substituted by prenyl and geranyl groups [23]. Diverse flavanoids are resulted by different positions of substituents or cyclization.

• Polyhydroxylated alkaloids

Polyhydroxylated alkaloids (alkaloidal imino sugars) are considered as analogs of saccharides in which the ring oxygen is replaced by nitrogen, and they are considered to have therapeutic potentials [24]. The genus *Morus* has attracted

much attention for its polyhydroxylated alkaloids, especially the principal α -glycosidase inhibitor—1-deoxyjirimycin (1-DNJ) [25].

• Diels–Alder-type adducts

Diels–Alder-type adducts, which formed by a Diels–Alder reaction between the α , β -olefinic moiety of a chalcone and an isoprene moiety, are the most representative compounds in the genus *Morus*. Nearly 90 Diels–Alder-type adducts have been isolated from *Morus* plants so far [23]. The structures of some bioactive Diels–Alder-type adducts that have been summarized by SBP [26] are shown in figure (a):

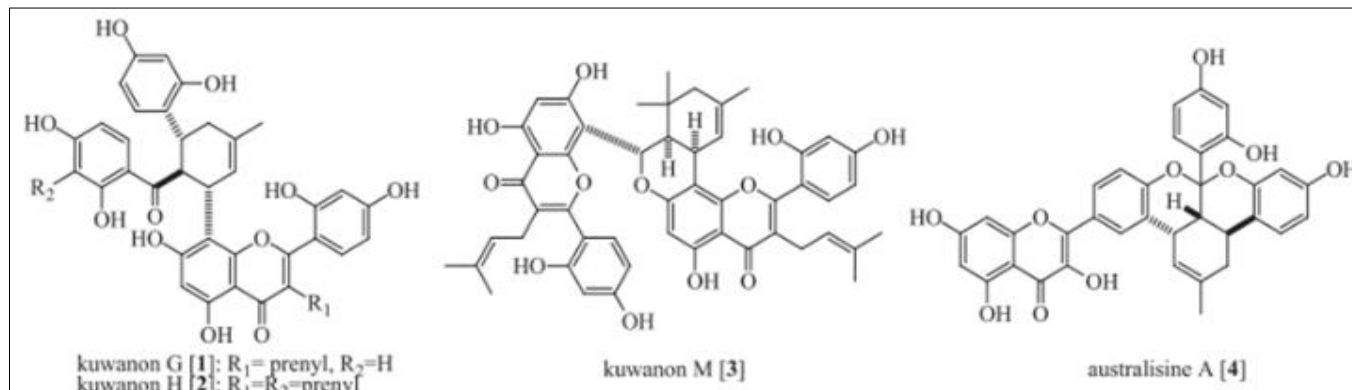


Fig 1a: Bioactive Diels–Alder type adducts

• 2-Arylbenzofurans and stilbenes

Morus plants are also rich sources of 2-arylbenzofurans and stilbenes, among which, 2-arylbenzo furans are commonly substituted by prenyl and geranyl groups. Diverse 2-arylbenzofurans are resulted by different positions of substituents or cyclization [23].

Pharmacological effects of Mulberry Plant

Antioxidative effects

Antioxidants inhibit the oxidation process in the plant and animal organisms and play a vital role in phyto physiological process. Antioxidants are widely used in the foods and drinks that are regularly served or consumed and have been systematically examined for the prevention of diseases such as cancer, heart disease and general sickness. Plants have developed specific anti-oxidative defense enzymes including catalase, peroxidase, polyphenol oxidase, ascorbate

peroxidase and glutathione reductase to control rapidly increasing ROS under various environmental stress conditions [27]. Antioxidant potential of fruits of four mulberry species namely *M. alba*, *M. nigra*, *M. indica* and *M. laevigata* were studied and the result indicated higher total phenol and alkaloid contents having values [(880±7.20) - (1650±12.25)] mg/100g fresh weight and [(390±3.22)- (660±5.25)] mg/100g fresh weight respectively. Based on the results, it was concluded that mulberry fruit is a potential source of food diet and radical scavenging activity [28]. The ripe fruits are abundant in polyphenolic antioxidants, which have greater scavenging capacity. It was also stated that anthocyanin, flavonoid, and phenolic acid, which has antioxidant activity, was observed having a carboxyl/carbonyl group help to bind hydrogen peroxide radicals and put an end to their radical chains (table 2), [29].

Table 2: Antioxidant components (mg/100g of fw) of mulberry

| Mulberry Genotypes | Ascorbic acid | Total flavonoids (mg QE/100gm) | Total Anthocyanin | Total phenolics (mg GAE/100gm) |
|---------------------------------------|---------------|--------------------------------|-------------------|--------------------------------|
| White Mulberry (<i>Morus alba</i>) | 21.8-24. | 29 | 24.7 ±0.3 | 142±6.1 |
| Red Mulberry (<i>Morus rubra</i>) | 16.1-19.4 | 219 | 289.2 ±0.9 | 435±4.2 |
| Black Mulberry (<i>Morus nigra</i>) | 4 11.3-22.4 | 276 | 206.1±1.8 | 481±7.1 |

(Source: Ercisli and Orhan, 2007)

The presence of anthocyanins provides fruit with a dark color that leads to antioxidant activity [30]. It has been found that mulberry fruits increase the strength of the anti-oxidative protecting system and diminish the damaging oxidative substances in the red blood cells (RBCs) of diabetes induced rats [31]. A study conducted on Low density lipoprotein (LDL) antioxidant activity and extracted some compounds from mulberry *M. alba* L. leaves. They found that quercetin 3-6-malonylglucoside and rutin are the chief flavonol glycosides in the mulberry leaves. Studies have reported that nine flavonoids isolated from mulberry leaves and examined for their free radical scavenging function were confirmed to be

antioxidative [32]. Ripen fruits are affluent with anthocyanins (polyphenol), which are tremendous antioxidant agents with stronger scavenging activity against free radicals, viz., 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), hydroxyls and superoxide anion radicals [33].

Hypoglycemic activity

Hypoglycemia is a disease in which the body's blood sugar content is too poor. From the centuries ago most of the countries of world practiced the traditional medicinal systems which are based on herbal plants. Mulberry was used in old

Chinese herbal medicine for reducing blood serum glucose [7]. Mulberry leaves are one of the most commonly used herbal remedies to treat hyperglycemia. Experiments on animal models proved that mulberry leaf extract possess antihyperglycemic, antioxidant and antiglycation activity [34]. It is effective in modulating the nitric oxide synthase expression in the hypothalamus of streptozotocin treated rats [35]. *M. rubra* leaf extract exerts its antidiabetic activity in streptozotocin induced diabetic rats by decreasing the fasting glucose levels, glycosylated haemoglobin and increasing the plasma insulin and C-peptide levels [69]. A study on mulberry leaf extracts and found that mulberry leaf extract acts as a natural inhibitor of α glucosidase due to deoxyojirimycin (DNJ) and its derivatives [8]. 1- Deoxyojirimycin (DNJ), a known antidiabetic principle from mulberry has been shown to inhibit intestinal glucosidases resulting in reduction of blood glucose [36].

Anti-inflammatory and antiallergic actions

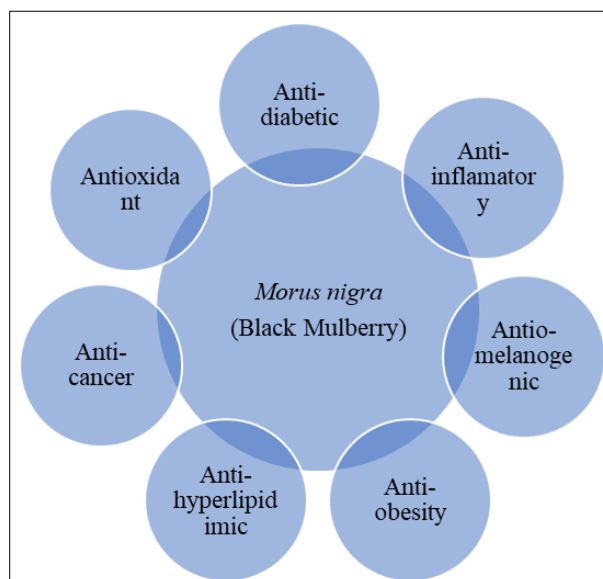
Anti-inflammatory is a term that refers to the ability of compounds to suppress swelling and inflammation is characterized as the body's combined effect of physiological protection mechanisms. Mulberry leaves were reported to having antipyretic and anti-inflammatory effects [37]. Also, the various flavonoids and related compounds isolated from *M. alba* exhibited anti-inflammatory effects [38]. They found that hot water extract from the bark of *M. alba* root has strong antihistaminic and antiallergic activity. Mulberry fruit flavonoid extract would inhibit ear swelling in mice. The levels of IL-1beta, including pro-inflammatory cytokines, TNF-alpha, nitric oxide, and interferon-gamma have steadily dropped after treatment of mulberry fruit extract in mice [39]. The principal anthocyanins found in mulberries are cyanidin 3-O-glucoside (C3 G), cyanide 3-Orutinoside (C3R), pelargonidin 3-O-rutinoside (P3R), and its antioxidant intensity is extremely high. All mulberry genotypes had an anti-inflammatory effect (measured by an inhibitory assay of cyclooxygenase (COX)), which was also compared to two commercial anti-inflammatory medicines.

Anticancer activity

Cancer is a serious public health problem worldwide. Many medicinal plants have anti-bacterial, anti-viral, anti-inflammatory, anti-cancer, immuno-stimulatory and antioxidant properties as well as compounds which effect specific organs. The methanolic extract of mulberry leaves shows efficient cytotoxic behavior against cancer cells. Mulberry also contains several anticancer compounds. *M. fructus* fruit extract induces cancer cell death *in vitro* and *in vivo*. The *in vitro* effect is due the cell death in an ROS dependent mitochondrial apoptotic pathway [40]. Phenolic compounds from *M. alba* induces *in vitro* anticancer activity in hepatoma cells by cell cycle arrest at G2-M phase and inhibition of topoisomerase II activity [41]. *M. alba* is a rich source of prenylated cyto-toxic flavonoids such as sanggenon, cyclomorusin, morusin, atalantoflavone, kaempferol etc. Morusin is the most potent among them with an IC₅₀ value of 0.64 μ M against HeLa cells [42]. New 2-arylbenzofuran derivatives (namely moracins of different structure from *M. alba* and wittifurans from *M. wittiorum*) with potent cytotoxic activity against different human cancer cell lines were identified recently [43]. A new galactose binding lectin was also purified from *M. alba* leaves with cytotoxic activity on human breast cancer (IC₅₀-8.5 μ g) and colon cancer cells (IC₅₀-16 μ g).

Anticancer activities of *Morus nigra*

Morniga M, a mannose-specific jacalin-related lectin from the bark of *M. nigra*, can preferentially trigger the proliferation and activation of human T- and natural killer (NK-) lymphocytes and dose-dependently induce cell death of α -CD3 activated T lymphocytes when compared with concanavalin A (Con A), a well-known mannose-specific legume leptin from *Canavalia ensiformis* [44]. Another brief research had demonstrated dose-dependent anticancer activity of n-hexane and aqueous methanol extract of *M. nigra* leaves against HeLa cell line (human cervical cancer), with IC₅₀ values of 185.9 \pm 8.3 μ g/mL and 56.0 \pm 1.7 μ g/mL, respectively [45]. Further the anticancer effects between fresh and dried fruit extracts of *M. nigra* have been compared on MCF-7 cell line (human breast cancer) [46].



Study results have shown that both ethanolic extracts dose- and time-dependently inhibit cellular growth of MCF-7 cells; exhibit apoptotic morphological changes in their cytoplasmic membranes, cell bodies, and nuclei; induce DNA fragmentations and single strand breaks; and decrease mitotic indexes, with better pharmacological properties in fresh fruit of *M. Nigra*. A study had also been done to evaluate the anticancer activities of *M. nigra* fruit extract on PC-3 cells (human prostate cancer) [47]. Dimethyl sulfoxide (DMSO) extract of *M. nigra* exhibited moderate cytotoxicity against PC-3 cells with an IC₅₀ value of 370.1 \pm 5.8 μ g/mL. It significantly increased the cell number at G0/G1 phase and decreased the cell number at S phase, indicating that *M. nigra* fruits inhibited the progression of the cell cycle at the G0/G1 phase. *M. nigra* fruit extract at a high dose (666 μ g/mL) significantly increased the number of necrotic, early apoptotic and late apoptotic cells compared to the untreated control group. It also dose-dependently decreased mitochondrial membrane potential and increased activities of caspase 3 and 7 (key mediators of apoptosis) in PC-3 cells.

Anticancer activities of *Morus alba*

As increase in the incidence of cancer, new studies are currently being performed with the aim of finding better and safer therapeutic agents. 33 Prenylated flavanone, 7, 2', 4', 6'-tetrahydroxy-6geranylflavanone separated from ethyl acetate extracts of *M. alba* root showed cytotoxic activity against hepatoma cells in rats with an IC₅₀ of 52.8 mg/mL [48]. Similarly, anthocyanins isolated from *M. alba* fruit showed

inhibitory effect on invasion and migration of highly metastatic A549 human lung carcinoma cells in dose dependent manner [49]. Methanolic extract obtained from *M. alba* and its sub fractions obtained from aqueous, butanol and chloroform fractions blocked or inhibited the NO production and significantly reduced the formation of tumor necrosis factor- α (TNF- α) in macrophages, which were LPS activated RAW2647 [50]. Further evaluation and clinical trials may reveal the therapeutic potential of *M. alba* against cytotoxic cells, which may help in finding a cheap and easily available source for treatment of cancer and decreasing invasiveness of cancerous cells.

Anti-diabetic activity

Mulberry leaves have long been used in Chinese medicine for the prevention and treatment of diabetes because as we now know it contains chemical compounds that suppress high blood sugar levels (hyperglycemia) following a carbohydrate-rich meal [51]. The result is insulin resistance a dangerous condition that, if unchecked, leads to type-2 diabetes. A research group in Japan has found that, white mulberry leaves contain compounds that inhibit these intestinal enzymes. Mulberry contains 1-deoxynojirimycin (DNJ) and some of its derivatives like alpha-glucosidase inhibitors that have been used as medicines to treat diabetes mellitus [52, 53].

M. nigra has also shown good antidiabetic effects on extracts and active constituents from some parts of this plant. Investigations have been done on the hypoglycemic efficacy of *M. nigra* leaf extracts and its cell suspension cultures treated with methyl jasmonate to induce accumulation of flavonoid contents in cell cultures [54]. Extracts from *M. nigra* leaves dose-dependently decreased plasma glucose concentrations and increased insulin levels up to 500 mg/kg/day in streptozotocin (STZ)-treated diabetic rats. Hydroethanolic extracts of *M. nigra* leaves also significantly decreased serum fasting and 2-h glucose concentrations (at dose of 50 mg/kg) and increased serum insulin level (at dose of 10 mg/kg) in nicotinamide-STZ-induced type 2 diabetic rats [70]. In addition, several phenolic compounds and isoprenylated flavonoids isolated from extracts of *M. nigra* twigs showed good antidiabetic activities, involving mechanisms of peroxisome proliferators-activated receptor gamma (PPAR γ) activation [55] and α -glucosidase inhibition [56]. Several studies in animals and humans have reported that mulberry or sericulture products containing DNJ suppress postprandial increases of glucose [57, 58]. It was reported that, certain nitrogen containing sugars were present in mulberry-leaf extract, notably one called 1-deoxynojirimycin, strongly inhibited the intestinal metabolism of disaccharides. Daily consumption of mulberry leaves improved hyperglycemia in diabetic rats and reduced oxidative stress in liver [59]. Beverages containing mulberry leaf (*Morus alba*) are believed to promote good health, especially people with diabetes in Thailand and the effect of long term administration of an ethanolic extracts of mulberry leaf was studied in blood glucose. Daily administration of 1g/kg of MA for six weeks decreased blood glucose by 22% which was comparable to the effect of 4v/kg insulin. Findings indicated that long term supplement of *M. alba* has anti-hyperglycemic effects in chronic diabetic rats [60].

Anti-obesity activity

Obesity is defined as abnormal or extravagant fat accumulation that extant a risk to health. Researchers suggested that mulberry extract might be beneficial in

preventing human diabetes by suppressing intestinal alpha-glucosidase activities [61]. The air dried leaves and fruits of ficus and mulberry were examined in ethanol and hexane extract and evaluated against hyperlipidaemia by estimating the rate limiting enzyme of cholesterol biosynthesis. A short term study on mice was conducted and exhibited an antagonistic action of mulberry extract on melanin concentrating hormone receptor, which help in decrease in body weight. They also suggested that ethanolic extract obtained from mulberry leaves showed antiobesity action on diet-induced mice [62]. Quercetin, the quantitatively major flavonoids glycoside in mulberry leaves effectively suppressed the blood glucose levels [8].

Neuroprotective activity

M. nigra owing to the presence of bioactive polyphenolic compounds such as anthocyanins, flavonoids, stilbene glycosides, lectins, oligosaccharides, unsaturated fatty acids, enzymes, and inhibitors possess pharmacological activities such as antihyperglycemic, anti-inflammatory, and neuroprotective effects [63]. Fruit extract of *M. nigra* has neuroprotective effect in inhibition of oxidative stress in the zebrafish brain owing to potent antioxidant properties of mulberry [64]. Mulberry fruit extract when tested against memory impairment and brain damage in animal model of vascular dementia, it was observed that mulberry fruit is potential natural cognitive enhancer and neuroprotectant [65]. Mulberry fruit contains the cyanidin-3-O- β -D-glucopyranoside which prevents the neuronal cell damage. They also suggest that mulberry fruit extracts having neuroprotective properties and prevent the cerebral ischemic damage caused by oxygen glucose deprivation (OGD) in PC12 cells [66]. The anaerobic treatment of mulberry leaves makes γ -aminobutyric acid to enhance the neuro-protection effect against *in vivo* cerebral ischemia [67]. The effectiveness of *M. alba* in improving the vascular reactivity of diabetic rats, the mechanism of which may associate with the abatement of oxidative stress [68].

Conclusion

Constantly seeing and being around plants helps people feel calmer and relaxed, thus decreasing levels of anxiety, increases attentiveness and memory, increases productivity. Reduces stress levels and boosts mood and parks creativity. Medicinal plants have long been utilized in traditional medicine and worldwide ethno-medicine. This chapter presented a glimpse of the current status of mulberry and its future trends in medicinal plant genomics, evolution, and phylogeny. Mulberry plant is a common herb that has been used in medicine for decades. Mulberry is currently used as medication in several countries due to its pharmacological properties. Mulberry is rich in phenols (resveratrol, oxy resveratrol, chlorogenic acid, mulberroside, maclurin and moracins), anthocyanins (cyaniding-3-glucoside, cyaniding-3-rutinoside, geranium-3- glucoside), non-anthocyanin flavonoids(rutin, quercetin, kaempferol-3-rutinoside), alkaloids (DNJ, fagomine) and polysaccharides possess pharmacological properties including antioxidant, anti-inflammatory, anti-carcinogenic, antibacterial, antiviral, anti-obesity, anti-apoptotic, anti-diabetic, neuroprotective activities. So, keep hoping it can relieve and/or regulate pathologies if it is included in an Journal of Natural Remedies Vol. 21, No. 5, 2020 43 ordinary diet. The industrialists have gained popularity from the further industrial processing of

mulberry by preparing various goods in the pharmaceutical, food, nutrition, cosmetic, and healthcare systems.

References

- Pihlanto A, Akkanen S, Korhonen HJ. ACE-inhibitory and antioxidant properties of potato (*Solanum tuberosum*). Food Chemistry 2008;109:104-112.
- Machii H, Koyama A, Yamanouchi H. Mulberry for Animal Production. Mulberry breeding, cultivation and utilization in Japan [M]. FAO Anim Prod Health Paper 2002.
- Arabshahi-Delouee S, Urooj A. Antioxidant properties of various solvent extracts of mulberry (*Morus indica* L.) leaves [J]. Foods Chemistry 2007;102:1233-124.
- Bae SH, Suh HJ. Antioxidant activities of five different mulberry cultivars in Korea [J]. LWT- Food Science and Technology 2007;40(6):955-962.
- Ercisli S, Orhan E. Chemical composition of white (*Morus Alba*), red (*Morus rubra*) and black (*Morus nigra*) mulberry fruits [J]. Food Chemistry 2007;103:1380-1384.
- Sreelatha S, Padma PR. Antioxidant activity and total phenolic content of *Moringa oleifera* leaves in two stages of maturity. Plant Foods and Human Nutrition 2009;64:303 -311.
- Andallu B, Suryakantham V, Lakshmi B, Reddy GK. Effect of mulberry (*Morus indica* L.) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes. Clin Chim Acta 2001;314:47-53.
- Katsube T, Imawaka N, Kawano Y, Yamazaki Y, Shiwaku K, Yamane Y. Antioxidant flavonol glycosides in mulberry (*Morus Alba* L.) leaves isolated based on LDL antioxidant activity. Food Chemistry 2006;97:25-31.
- Du Q, Zheng J, Xu Y. Composition of anthocyanins in mulberry and their antioxidant activity [J]. J Food Compos Anal 2008;21:390-395.
- Asano N, Oseki K, Tomioka E. N-containing sugars from *Morus Alba* and their glycosidase inhibitory activities [J]. Carbohydrate Res 1994;259:243-255.
- A. Tikader, K. Vijayan Assessment of biodiversity and strategies for conservation of genetic resources in mulberry (*Morus* spp.) Biorem. Biodiv. Bioavail 2010;4:15-27.
- Krishna H, Chauhan Mulberry N. (*Morus* sp.) Breeding of Underutilized Fruit Crops Part-II, Jaya Publishing House, Delhi 2015, 339-352.
- Chowdhury SN. Parthenogenesis, gynogenesis and androgenesis in silkworm, *Bombyx mori*: A review. Indian J Seric 1989;28:284-92.
- Vijayan K. The emerging role of genomic tools in mulberry (*Morus*) genetic improvement. Tree Genetics & Genomes 2010;6(4):613-25.
- Stuffness M, Douros J. Current status of the NCI plant and animal product program. J Nat. Prod 1982;45:1-14.
- Baker JT, Borris RP, Carte B, Cordell GA, Soejarto DD, Cragg GM *et al.* Natural product drug discovery and development: New perspective on international collaboration. J Nat. Prod 1995;58:1325-357.
- Zou Sheng-qin, Chen Wu. A review on chemical constituents, pharmacological activity and application of mulberry leaves, journal of Chemical Industry of Forest Products (Bimonthly) 2003-01 Table 1: Active Compounds in mulberry plant 2003.
- Andallu B, Varadacharyulu N. Control of hyperglycemia and retardation of cataract by mulberry (*Morus indica* L.) leaves in streptozotocin diabetic rats. Indian J Exp Biol 2002;40:791-5.
- Singhal BK, Khan MA, Dhar A, Baqual FM, Bindroo BB. Approaches to industrial exploitation of mulberry (mulberry sp.) fruits. Journal of Fruit and Ornamental Plant Research 2010;18(1):83-99.
- Yuan Q, Zhao L. The Mulberry (*Morus alba* L.) Fruit a Review of Characteristic Components and Health Benefits. Journal of Agricultural and Food Chemistry 2017;65(48):10383-94.
- Whelan J. The health implications of changing linoleic acid intakes. Prostaglandins, Leukotrienes and Essential Fatty Acids 2008;79(3-5):165-7.
- Le HD, Fallon EM, Kalish BT, de Meijer VE, Meisel JA, Gura KM *et al.* The effect of varying ratios of docosahexaenoic acid and arachidonic acid in the prevention and reversal of biochemical essential fatty acid deficiency in a murine model. Metabolism 2013;62(4):499-508.
- Yang Y, Tan YX, Chen RY, Kang J. The latest review on the polyphenols and their bioactivities of Chinese *Morus* plants. Journal of Asian Natural Products Research 2014;16:690-702.
- Watson AA, Fleet GWJ, Asano N, Molyneux RJ, Nash RJ. Polyhydroxylated alkaloids-natural occurrence and therapeutic applications. Phytochemistry 2001;56:265-295.
- Zhang N, Li YF, Zhou YM, Hou J, He Q, Hu XG *et al.* Rapid detection of polyhydroxylated alkaloids in mulberry using leaf spray mass spectrometry. Analytical Methods 2013;5:2455-2460.
- Hua Wei, Jing-Jing Zhu, Xiao-Qian Liu, Wei-Hong Feng, Zhi-Min Wang, Li-Hua Yan. Review of bioactive compounds from root barks of *Morus* plants (Sang-Bai-Pi) and their pharmacological effects, Cogent Chemistry 2016;2:1. 1212320,
- Singhania N, Puri D, Madhu SV, Sharma SB. Assessment of oxidative stress and endothelial dysfunction in Asian Indians with type 2 diabetes mellitus with and without macroangiopathy. QJM: An International Journal of Medicine 2008;101(6):449-455.
- Imran M, Khan H, Shah M, Khan R, Khan F. Chemical composition and antioxidant activity of certain *Morus* species. Journal of Zhejiang University Science 2011;11:973-980.
- Jiang D-Q, Guo Y, Xu D-H, Huang Y-S, Yuan K, Lv Z-Q. Antioxidant and anti-fatigue effects of anthocyanins of mulberry juice purification (MJP) and mulberry marc purification (MMP) from different varieties mulberry fruit in China. Food Chem Toxicol 2013;59:1-7.
- Beekwilder J, Jonker H, Meesters P, Hall RD, van der Meer IM, Ric de Vos CH. Antioxidants in raspberry: on-line analysis links antioxidant activity to a diversity of individual metabolites. Journal of Agricultural and Food Chemistry 2005;53(9):3313-20.
- Hong JH, Ahn JM, Park SW, Rhee SJ. The effects of mulberry fruit on the anti-oxidative defense systems and oxidative stress in the erythrocytes of streptozotocin induced diabetic rats. Nutrit. SC. 2004;7:127-132.
- Kim SY, Gao JJ, Lee WC, Ryu KS, Lee KR, Kim YC. Antioxidative flavonoids from the leaves of *Morus Alba*. Arch Pharm Res 1999;22(1):81-5.

33. Arfan M, Khan R, Rybarczyk A, Amarowicz R. Antioxidant Activity of Mulberry Fruit Extracts. *Int. J Mol. Sci* 2012;13:2472-2480.
34. Naowaboot J, Pannangpetch P, Kukongviriyapan V, Kongyingyoes B, Kukongviriyapan U. Antihyperglycemic, antioxidant and antiglycation activities of mulberry leaf extract in streptozotocin induced chronic diabetic rats. *Plant Foods for Human Nutrition* 2009;64:116-21.
35. Oh BK, Oh KS, Kwon KI, Ryu SY, Kim YS, Lee BH. Melanin-concentrating hormone-1 receptor antagonism and antiobesity effects of ethanolic extract from *Morus alba* leaves in diet-induced obese mice. *Phytotherapy Research* 2010;24(6):919-923.
36. Hansawasdi C, Kawabata J. Alpha-glucosidase inhibitory effect of mulberry (*Morus alba*) leaves on Caco-2. *Fitoterapia* 2006;77:568-73.
37. Chatterjee GK, Burman TK, Nagchaudhuri AK, Pal SP. Anti-inflammatory and antipyretic activities of *Morus indica*. *Planta Medica* 1983;48(2):116-119.
38. Chai OH, Lee MS, Han EH, Kim HT, Song CH. Inhibitory effects of *Morus alba* on compound 48/80-induced anaphylactic reactions and anti-chicken gamma globulin IgE- mediated mast cell activation. *Biol Pharm Bull* 2005;28(10):1852-1858.
39. Chen C, You LJ, Abbasi AM, Fu X, Liu RH, Li C. Characterization of polysaccharide fractions in mulberry fruit and assessment of their antioxidant and hypoglycemic activities *in vitro*. *Food & function* 2016;7(1):530-9.
40. Jeong JC, Jang SW, Kim TH, Kwon CH, Kim YK. Mulberry fruit (*Morus fructus*) extracts induce human glioma cell death *in vitro* through ROS-dependent mitochondrial pathway and inhibits glioma tumor growth *in vivo*. *Nutr cancer* 2010;62:402-12.
41. Naowaratwattana W, De-Eknamkul W, De Mejia EG. Phenoliccontaining organic extracts of mulberry (*Morus alba* L.) leaves inhibit HepG2 hepatoma cells through G2/M phase arrest, induction of apoptosis, and inhibition of topoisomerase IIa activity. *J Med Food* 2010;13:1045-56.
42. Dat NT, Binh PT, Quynh le TP, Minh CV, Huong HT, Lee JJ. Cytotoxic prenylated flavonoids from *Morus alba*. *Fitoterapia* 2010;81:1224-7.
43. Yang Y, Gong T, Liu C, and Chen RY Four New 2-Arylbenzofuran Derivatives from Leaves of *Morus alba* L. *Chem Pharm Bull* 2010;58:257-60.
44. Benoist H, Culerrier R, Poiroux G, Ségui B, Jauneau A, Van Damme EJ *et al*. Two structurally identical mannose-specific jacalin-related lectins display different effects on human T lymphocyte activation and cell death. *J Leukoc. Biol* 2009;86:103-114.
45. Qadir MI, Ali M, Ibrahim Z. Anticancer activity of *Morus nigra* leaves extract. *Bangladesh J Pharmacol* 2014;9:496-497.
46. Ahmed A, Ali M, El-Kholie E, El-Garawani I, Sherif N. 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.* 2016;2:352-361.
47. Turan I, Demir S, Kilinc K, Burnaz NA, Yaman SO, Akbulult K *et al*. Anti-proliferative and apoptotic effect of *Morus nigra* extract on human prostate cancer cells. *Saudi Pharm. J* 2017;25:241-248.
48. Kofujita H, Yaguchi M, Doi N, Suzuki K. A novel cytotoxic prenylated flavonoid from the root of *Morus alba*. *J Insect Biotechnol. Sericol* 2004;73:113-116.
49. Colonna M, Danzon A, Delafosse P, Mitton N, Bara S and Bouvier AM. Cancer prevalence in France: time trend situation in 2002 and extrapolation to 2012. *Eur. J Cancer* 2008;44:115-122.
50. Choi EM, JK Hwang. Effects of *Morus alba* leaf extract on the production of nitric oxide prostaglandin E2 and cytokines in RAW2647 macrophages. *Fitoterapia* 2005;76: 608-613.
51. Miyahara C, Miyazawa M, Satoh S, Sakai A, Mizusaki S. Inhibitory effects of mulberry leaf extract on postprandial hyperglycemia in normal rats. *J Nutr Sci Vitaminol* 2004;50:161-164.
52. Mudra M, Ercan-Fang N, Zhong L. Influence of mulberry leaf extract on the blood glucose and breath hydrogen response to ingestion of 75g sucrose by type-2 diabetic and control subjects. *Diabetes Care* 2007;30:1272-1274. 108.
53. Asai A, Nakagawa K, Higuchi O, Kimura T, Kojima Y, Kariya J *et al*. Effect of mulberry leaf extract with enriched 1-deoxyojirimycin content on postprandial glycemic control in subjects with impaired glucose metabolism. *J Diabetes Investigation* 2011;2(4):318-323.
54. Abd El-Mawla, A.M.; Mohamed, K.M.; Mostafa, A.M. Induction of Biologically Active Flavonoids in Cell Cultures of *Morus nigra* and Testing their Hypoglycemic Efficacy. *Sci. Pharm* 2011;79:951-961.
55. Xu LJ, Yu MH, Huang CY, Niu LX, Wang YF, Wu CZ *et al*. Isoprenylated flavonoids from *Morus nigra* and their PPAR agonistic activities. *Fitoterapia* 2018a;127:109.
56. Xu L, Yu M, Niu L, Huang C, Wang Y, Wu C *et al*. Phenolic compounds isolated from *Morus nigra* and their α -glucosidase inhibitory activities. *Nat. Prod. Res* 2018b.
57. Kimura T, Nakagawa K, Kubota H. Food-grade mulberry powder enriched with 1-deoxyojirimycin suppresses the elevation of postprandial blood glucose in humans. *J Agri Food Chem* 2007;55:5869-5874.
58. Nakamura M, Nakamura S, Oku T. Suppressive response of confections containing the extractive from leaves of *Morus Alba* on postprandial blood glucose and insulin in healthy human subjects. *Nutr Metab, (Lond)* 2009;6:29.
59. Kim GN, Kwon YI, Jang HD. Mulberry leaf extract reduces postprandial hyper glycemia with few side effects by inhibiting α -glucosidase in normal rats. *Journal of Medicinal Food* 2011;14:712-717.
60. Sun F, Shen LM, Ma ZJ. Screening for ligands of human aromatase from mulberry (*Morus alba* L.) leaf by using high-performance liquid chromatography/ tandem mass spectrometry. *Food Chem* 2011;126:1337-1343.
61. Asano N, Yamashita T, Yasuda K, Ikeda K, Kizu H, Kameda Y *et al*. Polyhydroxylated alkaloids isolated from mulberry trees (*Morus Alba* L.) and silkworms (*Bombyx mori* L.). *Journal of Agriculture and Food Chemistry* 2001;49:4208-4213.
62. Oh BK, Oh KS, Kwon KI, Ryu SY, Kim YS, Lee BH. Melanin-concentrating hormone-1 receptor antagonism and antiobesity effects of ethanolic extract from *Morus alba* leaves in diet-induced obese mice. *Phytother Res* 2010;24(6):919-923.
63. Padilha MM, Vilela FC, Rocha CQ, Dias MJ, Soncini R, Dos Santos MH *et al*. Anti-inflammatory Properties of

- Morus nigra* leaves. *Phytotherapy Research* 2010;24:1496-00.
64. Erkekoglu P, Baydar T. Acrylamide neurotoxicity. *Nutritional Neuroscience* 2014;17(2):49-57.
65. Bihnen NI, Albin RL. The cholinergic system and Parkinson's disease. *Behavioural Brain Research* 2011;221(2):564-73.
66. Kang Tong Ho, Jin Young Hur, Hyun Bok Kim, Jong Hoon Ryu, Sun Yeou Kim. Neuroprotective effects of the cyanidin- 3-O-beta-d-glucopyranoside isolated from mulberry fruit against cerebral ischemia. *Neuroscience Letters* 2006;391(3):122-126.
67. Kang Tong Ho, Hye Rim OH, Sun Moon Jung, Jong Hoon RYU, Mee Won Park, Yong Kon Park *et al.* Enhancement of Neuroprotection of Mulberry Leaves (*Morus alba* L.) Prepared by the Anaerobic Treatment against Ischemic Damage, *Biol. Pharm. Bull* 2005;29(2):270-274.
68. Naowaboot J, Pannangpetch P, Kukongviriyapan V, Kukongviriyapan U, Nakmareong S, Itharat A. Mulberry leaf extract restores arterial pressure in streptozotocin-induced chronic diabetic rats. *Nutr Res* 2009;29(8):602-8.
69. Sachdewa A, Khemani LD. Effect of *Hibiscus rosasinensis* Linn ethanol flower extract on blood glucose and lipid profile in streptozotocin induced diabetes in rats. *Journal of Ethnopharmacology* 2003;89:61-6.
70. AbouZid SF, Ahmed OM, Ahmed RR, Mahmoud A, Abdella E, Ashour MB. Antihyperglycemic effect of crude extracts of some Egyptian plants and algae. *J Med. Food* 2014;17:400-406. [Cross Ref] [PubMed] 48.