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ANTIOXIDANT AND MEDICINAL PROPERTIES OF MULBERRY (*MORUS SP.*): A REVIEW

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ABSTRACT

Mulberry is exclusively used for rearing silkworm due to the presence of unique chemo-factors like morin, β-sitosterol in leaves. Plant is a potential source for curing debilitating diseases. Flavonoids, anthocyanin and alkaloids present in the leaves, bark, root and fruits of mulberry play a pivotal role in containing free radicals and pro-oxidants generated in the body due to metabolism and phagocytosis. Though oxygen is much imperative for life processes, metabolism imbalance and generation of free radicals are prime reason for causing different ailments. The review reveals the wide range of important Pharmacological uses of mulberry including phytochemical composition, antioxidant, and medicinal properties. Present paper provides concrete evidence on the role of mulberry for antioxidation therapy and management of human diseases.

KEY WORDS: Anthocyanin, Antioxidants, β-sitosterol, Flavonoids, Mulberry, Phytochemical.

INTRODUCTION

Mulberry is a perennial and woody plant, belongs to the family *Moraceae* and genus *Morus* native of China. Mulberry plants showing fast growth and short proliferation period, a deciduous plant grows under various environmental conditions i.e., tropical, subtropical and temperate.[1] Plants are preferred due to foliage yield since leaves constitute the only food of

silkworm *Bombyx mori* L. for manufacturing silk and used for various activities due to their strong environment adaptability.[2] About 12-16 species of genus *Morus* are found in sub-tropical, warm and temperate regions of Asia, Africa and North America.[3] Mulberry plant is one of the conventional herbs used in medicine Since time immemorial due to its chemical composition and pharmacological function. Most parts of mulberry plants are used as medicine in Chinese and Indian medicine.[4] In European countries mulberry is grown for fruit production and also used as vegetable in different parts of the World, while in Japan mulberry leaves are used for tea and powder juice.[5,6] Mulberry is commonly used as silkworm diet and an alternative medicine and reported to contain many antioxidative flavonoid compounds and free radical scavenging effects.[7] It contains many phenolics that can reduce cardiovascular disease.[8] Mulberry has also been reported to have hypoglycemic, hypolipidemic and antioxidant effects.[9] Mulberry showed high antioxidant activity in LDL oxidation assay.[10] Phytochemical composition and nutritional potentials of mulberry varieties have studied worldwide.[11-13] Mulberry leaves are used as infusion in Asian countries most common in Japan and Korea due to the presence of steroids, flavonoids, amino acids, vitamins, triterpenes and other trace elements show valuable effects.[14]

Mulberry leaves have been used for years to treat hyperglycemia, inflammation, cough, hypertension, cancer and fever.[15] Because of its good therapeutic activity and low toxicity, *Morus alba* has been extensively used in conventional Chinese medicine.[16] *Morus alba* is reported to have neuroprotective, skin tonic, antioxidant, anti-hyperglycemic, antibacterial, antihypertensive and anti-hyperlipidemic activities.[17-18] In many tropical countries, sericulture is being practiced to rear silkworm to produce silk fibre. In India, the word 'SERI' is popularly known as Self Employment Remunerative Industry with minimum investment and less profitability and provides employment throughout the year. Nearly 60% of production cost of silkworm cocoon is incurred by mulberry leaf production.[19] Protein content of leaves and young stem varies from 15% -28% depending on the variety. Economic viability of combining sericulture with dairy production produced excellent results.[20] Some species like *Morus laevigata*, *Morus rubra*, *Morus nigra* and *Morus alba* are grown for their leaves and fruits having medicinal importance. Wide range of medicinal activities have been credited to the different parts of mulberry plant, leaves of *Morus alba* are dried and used in infusions in most of the Asian countries.[21] Main aim of the present review is to focus on antioxidant and medicinal properties of mulberry in curing different diseases and finally to

draw some conclusion that, researchers can pay their attentions to explore different parts of mulberry plant available in nature abundantly.

Chemical Composition Of Mulberry

Mulberry leaves and fruits contained many bioactive components such as alkaloids, anthocyanins and flavonoids.[22-23] Mulberry leaves are rich in alkaloids including 1-deoxynojirimycin (DNJ), the most potent glycosidase inhibitor that decreases blood-sugar levels.[24-25] Resveratrol (trans-3,4^1,5-trihydroxystilbene) and Oxyresveratrol (trans-2,3^1,4,5^1-tetrahydroxy stilbene) are hydroxystilbenes found in mulberry.[26] This bioactive substance is a potent neuroprotectant and has cardioprotective effect.[27] Oxyresveratrol has an inhibitory effect on tyrosinase to limit melanin biosynthesis and used as cosmetic material and medical agent for hyper pigmentation disorders.[28-29] Anthocyanins are a group of natural phenolic compounds responsible for colouring of fruits, flowers and leaves. They are the best source of health benefits as antioxidant and anti-inflammatory compounds.[30] Anthocyanin has high inhibitory ability on lipid oxidation and mulberry anthocyanin extract has antimetastatis activity to inhibit migration of B16-F1 cells.[31-32] Flavonoids are commonly occurred in plant kingdom and mulberry found to contain at least four flavonoids including rutin. Flavonoids have been recognized to possess anti-inflammatory, antioxidant, antiallergic, antithrombotic, hepatoprotective, antiviral and carcinogenic activities in human beings.[33] Plants also include nutritive compounds like crude protein, crude fat, mineral elements and total sugars to evaluate the correlation between the active components and their antioxidant activities.

Antioxidant Activities Of Mulberry

Free radicals are chemical species possessing an unpaired electrons considered as fragments of molecules are generally very reactive. They are produced continuously in the cells either accidental by-products of metabolism or deliberately, for example, phagocytosis.[34] The potentially reactive derivatives of oxygen, ascribed as Reactive Oxygen Species (ROS) such as superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH) and alkoxyl radicals (RO) are routinely generated at low levels by plant cells.[35] Under normal circumstances, production and destruction of ROS is well regulated in cell metabolism and there is equilibrium between the ROS generated and antioxidant enzymes present.[36-37] However, exposure of plants to adverse environmental conditions, ROS production will overcome scavenging systems favouring the ROS upsurge that culminate in oxidative stress.[38] In these conditions, ROS attack vital bio-molecules and disturb the cell metabolism

and ultimately cell causes its own death. 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.[39] To avoid hazards associated with oxidative stress, antioxidants in the form of food supplement is required by the human body.[40]

Antioxidant activity of *morus* leaf was tested using silica gel column chromatography and isolated constituents were analyzed in vitro for antioxidant activity against DPPH and ABTS radicals.[41-42] Four flavonoids were isolated and all these compounds showed DPPH and ABTS radical scavenging activity.[43] Antioxidant potential of fruits of four mulberry species namely *Morus alba, Morus nigra, Morus indica* and *Morus 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.[44] Methanolic extract of fruit showed a correlation with total phenolic constituents of the respective fruits. Ethanol and hexane extracts were investigated in an in vitro air dried leaves and fruit juice of some Ficus and Morus species.[45] Antioxidant activity was evaluated by reduction of DPPH radical. *Ficus mysorensis* (hexane extract) recorded antioxidant effects. Different compounds of *Morus alba* were isolated using column chromatography and compound was isolated called 'albosteroid' showed significant dose dependent reversal of ethanol diminished activity in antioxidant enzymes.[46-47] White mulberry stem bark, root bark, leaves and fruit content of methanolic extract was evaluated by in vitro standard method using spectrophotometer.[48] Among the extracts, stem bark showed highest antioxidant activity and hence, plant could serve as effective free radical inhibitor. Antioxidant effect of *Morus bombycis* Koidzumi roots and the presence of purified compound 2,5-dihydroxy-4,3-di-trans-stilbene displayed dose dependent superoxide radical scavenging activity as assayed by the Electron Spin Resonance (ESR) technique. Results demonstrated that, compound is a potent antioxidant to scavenging the radicals.[49] Eight phenolic compounds were purified from *Morus yunanensis* stem bark using silica gel, Sephadex LH-20 and RP-18 by column chromatography. Out of eight phenolic compounds purified, mulberrofuran, albanol B, moracin M and 2^1,5^1,2,4-tetrahydroxy-4-stilbene showed potential antioxidation activities.[50] Mulberry leaves treated with UV-C found to contain three different phytoalexins namely moracin C, moracin N and chalcomoracin and they are capable of scavenging superoxide anion.[51] Three different extracts of *Morus nigra* (fruit

juice, hydrochloric acid and polyphenols) on haemoglobin glycolysation, peroxidative damage to human erythrocytes were studied. All the three extracts inhibited haemoglobin glycolysation and haemolysis of human erythrocytes. Results suggest that *Morus nigra* has protective action against bio-membranes and biomolecules.[52] Different parameters in n-dimensional space with different fruit wines demonstrated the importance of bilberry, blackberry and black mulberry wines as natural antioxidants and colourants.[53]

Anthocyanin content and peroxyl radical scavenging capacities using HPLC with ESI-MS and diode array detection in twenty seven mulberry cultivars of mulberry fruits *Morus artropurpurea* Roxb. using electrospray ionization mass spectra were determined and Pro-anthacyanidin was quantified and selected mulberry fruits revealed significant amount of lutein and delta and gamma tocophenols but low alpha-tocophenol.[54] Uptake of Anthocyanin extracted from *Morus nigra* and was orally administered to Winstar rats. Their concentration was determined in plasma, kidney and gastrointestinal tract. The glycosylated forms showed maximum concentration at 15 minutes after oral administration both in plasma and kidney and cyanidin-3-glucoside and cyanidin-3-rutinoside were found in plasma.[55] Anthocyanin is present in mulberry extract and it is a natural colorant constituent for plant.[56] Anthocyanins showed antioxidant activity by scavenging the peroxyl radicals in trapping reaction. Anthocyanin glycosides were no longer detected in GI tract after 8 hours of administration. Anthocyanins were transported across the erythrocyte by sodium-dependent glucose transporter.[23,57] The bioactive constituents isolated from *Morus alba* such as leachianone and kuwanon-G showed antibacterial activities and 1-deoxynojirimycin (DNJ) showed α-glycosidase inhibitors activity. Likewise *Morus alba* extract and its other compounds usually flavonoids have antioxidant properties by scavenging free radicals and protect many organs from oxidative stress.[58]

Medicinal Properties Of Mulberry

Mulberry leaves containing sugars, rutin, quercetin, volatile oil, amino acid, vitamins and microelements that have so many pharmacological activities such as reducing blood glucose, antihyperlipidemia, hypertensive, bacteriostatic and antivirus.[59] Bio active compounds in different species of mulberry can enhance lifespan.[60] Different pharmaceutical properties of mulberry plants are reviewed by many scientists and they have reported that, many biochemical compounds such as Moranoline, Albafuran, Albanol, Morusin, Kuwanol, Calystegine and Hydroxymoricin are isolated from mulberry plants play an important role in

pharmaceutical industry.[61-63] Medicinal properties of mulberry plants are identified for their profitable medicinal value and therefore attracted the attention of pharmaceutical research and industry.

In herbal medicine, fruits, leaves, flowers, stems, bark and roots are used to treat a number of conditions. Mulberry herbal supplements have many names including noni, nhau, mengkudu, hog's apple, wild pine, caribe and nono. Each of these names refers to products derived from mulberry trees and has similar benefits as well as risks. Mulberry is an excellent source of potassium used by the body to create energy necessary to power cells. Additionally, elements in mulberries have potential to reverse cell damage and stimulate the immune system.[64] Mulberry has potent chemical constituents provide homeo-therapies for various ailments in human beings. In India the plant is affectionately called "Kalpavruksha" for its benevolence nature and the presence of secondary metabolites like phenols, flavonoids and anthocyanins play a pivotal role as scavengers for oxidants present in body.[65] Different parts of mulberry are used to protect the body and to control oxidative stress, diarrhea, constipation, nausea, intestinal worms, sinusitis, throat soreness, urinary tract infections, diabetes, fever, asthma, hyperglycemia, inflammation, kidney disorders, cancer, cataracts, cyto and hepatoprotectivity, vaginal discharge or menstrual problems, depression and migraines.[66] Mulberry is also used to prevent strokes and heart disease and to reduce signs of aging for its role in anti-oxidation. Mulberry can nourish and promote production of body fluid. Person having body fluid deficiency often feels their mouth parched and tongue scorched. A person can take one ounce of ripe mulberry fruits every day. This product has a faint scent and sweet taste, suitable for people of all ages. Brew water to take dry fruit, using 10 grams each time. Person having dry eyes and uses their eyes a lot during work can drink mulberry juice that can nourish the body fluid and strengthen eye sight. Mulberry contains plentiful nutritious elements such as minerals and vitamins; it can cure chronic diseases of the digestive tract, promote gastric juice secretion, strengthen the ability for digesting and assimilating, improve the appetite and eliminate abdominal distention and constipation. Mulberry is very well suitable for chronic gastritis, hepatitis and Alzheimer diseases.[67-68]

Flavonoids

Flavonoids are chemically poly phenolic secondary metabolic compounds universally distributed in green plant kingdom located in cell vacuoles. Flavonoids are responsible for colour, aroma of flowers to attract pollinators, spore germination, growth and

development of seedlings. Stress due to biotic and abiotic factors could be protected by flavonoids.[69] Flavonoids are structurally derived from the parent substances flavones commonly found in cell sap of young tissues of higher plants.[70] Nine flavonoids isolated from *Morus alba* leaves on the basis of spectroscopic analysis and chemical structure. Among them, Quercetin exhibited significant radical scavenging effect on 1,1-diphenyl-2-picrylhydrazyl, absorption and bioavailability of Quercetin in mulberry and is most significant for antioxidant potential of mulberry plant.[18,71-72] The leaves of mulberry contains higher amount of Quercetin responsible for reduction of oxidation process in vivo and in vitro.[73-76] Rats were fed with extract (15g/rat/day) or Sutin (135µg/rat/day) for 2 weeks. Phenyl acetic acid a microbial metabolite of Quercetin was detected in the wine of test samples and also present in fecal samples. Total antioxidant activity in body was observed due to microbial metabolites present in Quercetin. Four flavonols were determined by HPLC and in oxygen radical absorbance capacity assay. Quercetin had the highest antioxidant activity that depends upon permeability across cell membrane and peroxyl or hydroxyl scavenging capacity.[77] Evaluation of Korean alcoholic beverage 'Yakju' enriched with mulberry and was observed during 15 days of fermentation. Antioxidant property of the beverage increased due to fermentation of flavonoid and total polyphenol contents present in leaves.[78] RT-PCR results indicated that flavonoids increase the UV shielding activity of cocoons. In *Bombyx mori* dietary flavonoids are metabolized and accumulate in cocoon causing green colouration. This helps to understand the mechanism of metabolism, uptake and transport of dietary flavonoids which have variety of biological activities in animals and human health.[33] By employing voltammetry techniques, volatile substance present in *Morus nigra* mulberry tea was tested for antioxidant activity in chromatography assays and results showed that, consumption of antioxidant beverages prepared from mulberry may be beneficial to human health.[79-80] Fractionation of ethanolic extract of stem bark of *Morus Yunanensis* result in isolation of 2 flavones, out of that Yunanensin A showed moderate antioxidant activity.[31]

Oxidative Stress

It is the imbalance between pro-oxidants and antioxidant mechanisms. This results in an excessive oxidation metabolism. This stress can be due to several environmental factors such as exposure to pollutants, alcohol, medication, infection, poor diet, toxins, radiations etc. Oxidative damage to DNA, protein and other macromolecules may lead to a wide range of human diseases most notably heart disease or cancer. *Morus alba* leaves has been used as

food supplement in patients with certain diseases in that, the oxidative stress induced cellular injury in pathologically involved rats.[81] Eight week old Lewis rats immunized with cardiac myosin were fed with normal diet containing 5% mulberry leaf powder and examined on 21st day. Mulberry leaves significantly decreased oxidative stress and afford protection against endoplasmic reticular stress mediated apoptosis.[75,82] When mice were subjected to water immersion, retain stress at 25°C for 8 hours, the plasma lipid peroxide level performed after 12 hours was almost doubled. After administration of mulberry juice, one or two weeks before stress binding, the lipid peroxidation was completely blocked. ESR spectroscopy revealed that, anti-stress activity of mulberry juice in vitro may be derived from radical scavenging activity.[83]

Hypolipidemic Activities

Morus alba known for its medicinal properties and traditionally used for hypolipidemic activities. Ethanol and hexane extracts of *Ficus mysorensis* were evaluated and estimated in vitro in hypercholesterolemic rats. Hexane fraction was chromatographed and six compounds were isolated and these compounds recorded hypolipidemic effects.[46] Consumption of MRBF-2 fraction of *Morus alba* L. root bark (70% alcohol extract) may act as potent hypocholesterolemic nutrient and inhibition of LDL antherogenic modifications and lipid peroxidase formation in hypocholesterolemic rats.[84] Moracin present in mulberry leaves are capable of inhibiting lipid peroxidation that strongly indicates their role as scavenger.[51]

Hepatoprotective Activity Of Mulberry

Morus alba contains flavonoids, coumarine and stilbene that possess hepatoprotective activity.[85] 2,5-dihydroxy-4,3^1-di-trans-stilbene purified from *Morus bombycis* Koidzumi roots against CC14 induced liver damage in rats. *Morus nigra* fruit has protective action against peroxidative damage to bio membranes and biomolecules.[86] The compound is a potent antioxidant with liver protective action against CC14-induced hepatotoxicity.[87] Hepatoprotective potential of *Morus alba* leaves extract against hepatotoxicity induced by CCl4 was studied and results revealed that, alcoholic extract and aqueous extract showed significant protective potential against the toxicity induced by CCl4. However, the alcoholic extract showed noteworthy hepatoprotective effect revealed by biochemical and histopathological parameters.[88] Liver protective effect of *Morus alba* and *Calendula officinalis* extracts were examined against CCl4 induced toxicity in isolated rat hepatocytes. *Morus alba* extract prominently reduced alanine amino transferase (ALT), aspartate

aminotransferase (AST) and lactate dehydrogenase (LDH) levels and maintained integrity of isolated hepatocytes. Results confirmed that, these plants have significant hepatoprotective effects against hepatotoxicity induced by CCl4.[89] Moracin-a flavonoid present in *Morus mesozygia* twigs displayed significant hepatoprotective activity.[55] EtOH extract of *Morus alba* showed free radical scavenging activity and hepatoprotective nature of cudraflavones and oxyresveratrol.[90]

Anti-Inflammatory Properties Of Mulberry

Morin is a flavonoid present in mulberry exhibited considerable anti-inflammatory activity. Role of morin on the disposition of CsA in lymphoid and non-lymphoid tissues and immune cells in mice was studied. Decreased level of CsA in tissues was correlated to increased doses of Morin.[91] Flavonoids isolated from *Morus nigra* and *Morus alba* bark showed potent anti-inflammatory activity.[46,92] Natural antioxidant curcumin and an extract of *Morus alba* leaves have protective effect on resistin activated human endothecial cells and was determined by RT-PCR and western blot. *Morus alba* and curcumin target resistin induced human endothecial cells activation may represent therapeutic agents in vascular diseases mediated by resistin.[93] Stem bark of *Morus wittiorum* extracted with 95% EtOH and fractionalized using column chromatography. Six flavonoids and three stilbenoids were isolated exhibited anti-inflammatory or cytotoxic activities.[94] Resveratrol is a polyphenol compound and an anti-inflammatory agent found in *Morus alba* fruits, IL-8 plays a central role in the initiation and maintenance of inflammatory response. IL-8 production was measured by ELISA and RT-PCR. Resveratrol inhibits IL-8 secretion by blocking MAPK phosphorylation and NF-Kappa B activation. Resveratrol modulates THP-1 cell activation under inflammatory conditions. Fractionations of the ethanolic extract of *Morus yunanensis* stem bark and isolated Yunanensol showed potent anti-inflammatory activity.[50] Methanolic extract of *Morus alba* leaves capable of suppressing inflammatory mediators.[28] Ethyl acetate fractions of *Morus alba* significantly decreased NF-Kappa B luciferase activity and also secretion of NO and PGE in LPS/IFN-gamma stimulated peritoneal macrophages. Anti-inflammatory properties of MA extract might be resulted from the inhibition of pro-inflammatory mediators (NO and PGE).[27]

Atherosclerosis Effects Of Mulberry

It was investigated that, the anti-atherogenic effect of mulberry leaf extracts and polyphenolic extracts contained polyphenols including quercetin(11.70%), naringenin(9.012) and

gallocatectin gallate(11.02%). Both the extracts inhibited oxidation and lipid peroxidation of LDL and polyphenolic extract was more potent. Mulberry leaf polyphenolic extract potentially could be developed as anti-atherogenic agent. Atherosclerosis involves proliferation and migration of Vascular Smooth Muscle Cell (VSMC).[95] Leaf extract contains polyphenols(44.82%) including gallic acid, protacateonic acid, catechin, gallocatechin gallate, caffeic acid, rutin and quercetin inhibit the migration of VSMC by blocking small GTPase and Akt/NF-KappaB signal.[9] Two extracts MWE (Mulberry Water Extract) and MAC (Mulberry Anthocyanin Extract) exhibited antioxidation and antherosclerogensis abilities in vitro and they observed that MWE and MAC could decrease macrophage death induced by oxidative LDL and also inhibit the formation of foam cells and anthocyanins components in mulberry extracts could prevent atherosclerosis.[96] Apolipoprotein deficient mice fed with diet containing 12 ML powder from 6 weeks of age and mice were sacrificed after 12 weeks. Susceptibility of plasma lipoprotein into oxidation was assessed using diene formation. A significant increase in lag time of lipoprotein oxidation was detected in mulberry leaf group compared with control group. Mulberry leaf group showed 40% reduction in atherosclerotic lesion size in aorta compared with the control.[97] Male mice aged 8 week were randomly assigned to 4 groups (control, Quercetin, Quercetin 3-(6-malonylglucoside) (Q^3MG) and mulberry). Control group was fed with antherogenic diet containing 3g cholesterol and 15g cocoa butter/100g. The other experimental groups were fed same antherogenic diet supplemented with 0.05g Quercetin /100g for Quercetin group 0.05g Q^3MG/100g for Q^3MG group and 3g dried mulberry leaf powder/100g for mulberry group. Mice were fed their respective diet for 8 weeks. Susceptibility of LDL to oxidative modification was significantly decreased in Q^3MG and mulberry treated mice compared to that of control mice.[73]

Effect Of Mulberry In Neurological Disorders

The protective effects of 70% ethanol extract of mulberry fruit against neurotoxicity in in vitro and in vivo Parkinson's disease models were examined. Results revealed that, mulberry fruits significantly protected the cells from neurotoxicity in a dose dependent manner.[98] The beneficial effect of mulberry extract (ME) rich in phenolics and anthocyanins were evaluated. Six month old senescent- accelerated mice [$SAMP_8$] and [$SAMR_1$] were fed a basal diet supplement with 0.18% and 0.9% mulberry extracts for 12 weeks. Mice fed with ME supplement showed significantly less amyloid beta protein and showed improved learning and memory ability. ME treated mice showed higher antioxidant enzyme activity and less

lipid oxidation in both liver and brain as compared to control mice.[99] Alzheimer's disease is other common neurodegenerative disorder. Use of mulberry leaves reduced the risk of this disease and mulberry leaf extract provides a significant source of treatment for Alzheimer's disease by inhibition of amyloid beta-peptide (1-42) fibril formation. As a result attenuation of the neurotoxicity induced by amyloid beta-peptide (1-42) was observed.[100] Neurodegeneration is mostly caused by free radicals production. Neurological disorders such as Parkinson's and Alzheimer's diseases have been due to the depletion of gamma amino butyric acid (GABA) in brain. The studies suggested that mulberry isolated compounds can be used as neuroprotective agents for neurodegenerative diseases treatment.[101]

Role Of Mulberry In Cancer

Cancer is one of the major causes of death in animals specially felines and canines. It was observed that longer the life of animals, the chance of exposure to carcinogenic agents increased. Because of high incidence of cancer, new studies are currently being performed with the aim of finding better and safer therapeutic agents.[86] Prenylated flavanone, 7, 2′, 4′, 6'-tetrahydoroxy-6-geranylflavanone separated from ethyl acetate extracts of *Morus alba* root showed cytotoxic activity against hepatoma cells in rats with an IC50 of 52.8 mg/mL.[102] Similarly, anthocyanins isolated from *Morus alba* fruit showed inhibitory effect on invasion and migration of highly metastatic A549 human lung carcinoma cells in dose-dependent manner.[103] Methanolic extract obtained from *Morus 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-a (TNF-a) in macrophages, that were LPS activated RAW2647.[28] Further evaluation and clinical trials may reveal the therapeutic potential of *Morus alba* against cytotoxic cells that may help in finding a cheap and easily available source for treatment of cancer and decreasing invasiveness of cancerous cells. Stem bark of *Morus wittiorum* was extracted with 95% ethyl alcohol, flavonoids and quercetins present in the bark exhibited selective cytotoxicity against human ovarian cancer and human gastric cancer.[94] Mulberry leaves contain wide range of polyphenols and mulberry fruit extracts result in human glioma cell death in vitro through RoS dependent mitochondrial pathway and induction of apoptosis.[104] Tumourigeaesis in Swiss albino mice was studied and the efficacy of *Morus indica* (Methanolic extract) was also evaluated by in vitro by studying the inhibition activity and level of aryl hydrocarbon hydrocylase, cytochromes P_{450}, DNA sugar damage in calf thymus. Significant increase in antioxidant enzymes ($P<0.001$) and concomitant decrease ($P<0.001$) in cutaneous malondialdehyde level

were observed at three doses of plant extract (2.5, 5.0 and 7.5mg/kg). The extract may be useful as a therapeutic agent for cancer control as it blocks or suppresses events associated with carcinogenesis.[105] Leaf extracts of *Morus alba* L. protected erythrocytes from free radicals induced haemolysis. Extract significantly prevented gastric mucosal injury induced by ischemia reperfusion in rats when given orally at doses of 0.25 and 0.50g/kg/day for 3 consecutive days. Results indicated that, *Morus alba* leaf extract possesses cytoprotective activity due to presence of flavonoids against free radical-induced cell injury.[81]

Importance Of Mulberry In Diabetics

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.[106] Controlling blood sugar (glucose) levels is vitally important. When these levels rise sharply, as they do after ingesting foods with a high glycemic index such as potatoes or sweets, body responds by producing more insulin to deal with the overload. But if this demand for more insulin occurs too strongly too often, the ability of the pancreas to produce enough insulin may become impaired and our cells may become resistant to insulin as it tries to do its job of facilitating glucose transport through the cell walls. The result is insulin resistance a dangerous condition that, if unchecked, leads to type-2 diabetes. Its primary cause is obesity. Generally speaking, if you are obese, your risk for diabetes is high; if not, it's low (unless you happen to have a genetic predisposition for diabetes).[61] 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.[107-108] Alpha-glucosidase enzymes in the intestinal lumen and in the brush border membrane have a main role in carbohydrate digestion of starch and oligosaccharides to monosaccharides before they are absorbed.[109] Suppressing the activity of such digestive enzymes would delay the degradation of starch and oligosaccharides, this would in turn decrease the absorption of glucose and consequently suppress postprandial blood glucose level elevation.[110-112]

Recently, several studies in animals and humans have reported that mulberry or sericulture products containing DNJ suppress postprandial increases of glucose.[24,113] 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

(especially sucrose), thereby restricting the amount of monosaccharides entered circulation. They also found that, pretreating the rats with mulberry extract before feeding them carbohydrates significantly suppressed normal postprandial (after-meal) rise in blood glucose levels. This beneficial effect occurred in a dose-dependent manner. Doses were however very large: 0.1-0.5g/kg of body weight for a 70-kg (154-lb) human would be 7-35g. (A lower dose 0.02g/kg, corresponding to 1.4g for a human was ineffective). Nonetheless, researchers suggested that mulberry extract might be beneficial in preventing human diabetes by suppressing intestinal alpha-glucosidase activities.[114] The air dried leaves and fruits of ficus and mulberry were examined in ethanol and hexane extract and evaluated against hyperlipidemia by estimating the rate limiting enzyme of cholesterol biosynthesis. *Ficus mysorensis* (hexane extract) was evaluated in vivo by lipid profile estimation in hypercholesterodemic rats. Hexane fraction was chromatographed and six isolated compounds were identified. *Ficus mysorensis* recorded hypolipidemic activity.[45,115] Effect of *Morus nigra* (Aqueous extract) on artificially induced diabetic and non-diabetic rats and recorded the lipid profile. In diabetic rats, plant treatment caused reduced MDA, cholesterol, triglycerides and VLDL levels. *Morus nigra* treatment reduced the incidence of internal anomalies in offspring from diabetic rats.[82] Mulberry therapies were conducted on type-2 streptozoticin induced diabetic rats showed improvement in fasting blood glucose levels. Quercetin, the quantitatively major flavonoids glycoside in mulberry leaves effectively suppressed the blood glucose levels.[75] Daily consumption of mulberry leaves improved hyperglycemia in diabetic rats and reduced oxidative stress in liver.[116] 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 *Morus alba* has anti-hyperglycemic effects in chronic diabetic rats.[66,117] *Morus nigra* leaves were collected from different locations of Jordan and used for the treatment of diabetic symptoms. It was determined by DPPH and ABTS assays in relation to the total phenolic contents of fruit, roots and shoots of mulberry. *Morus nigra* extract and its potential use in radical scavenging made Jordanian population to extensively use the plants as a traditional anti-diabetic agent.[118] Antioxidant role of mulberry (*Morus indica*) on the various antioxidant enzymes in rat erythrocytes like glutathione per-oxidase, glutathione reductase, glutathione-S-transferase and super oxide dismutase observed in uncontrolled diabetes were improved by treating with mulberry very efficiently.[62,119]

CONCLUSION

For the eternal health, longevity and remedy, to remove pain and discomfort, fragrance, flavor and food, all over the world mankind depend upon the plants to meet their demands. Medicinal plants still play important role in emerging and developing countries. Mulberry plant is one of the important traditional herbs widely used in medicine from centuries ago. It is a rich source of flavonoids and other compounds that showed antimicrobial potential and free radical scavenging activity. Due to its pharmacological properties, all parts of plant are used as medicine. Mulberry is proved in protecting liver, improving eyesight, facilitating discharge of urine, lowering of blood pressure, anti-diabetic and weight controlling in human beings. Mulberry leaves are rich in protein and widely used as silkworm food, in food formulations and also have neuroprotective functions can be used against neurodegenerative disorders such as Alzheimer and Parkinson. Other useful effects such as immune-modulation and chemo-protective properties need further exploration by researchers. It is the need of the hour to explain medicinal values of mulberry by scientists.

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