Mulberry is a fast growing woody perennial plant belonging to the family Moraceae. These plants gained attention since time immemorial due to its pharmacological and economic value. Use of mulberry leaves in sericulture has been reported in the ancient Chinese literature. Medicinal properties of this plant have been depicted in the ancient literature of Ayurveda. Some of the ayurvedic preparations use fruits, leaves, roots, bark or latex to administer various diseases. Extensive research done during the past few decades thrown light on the active principles present in mulberry. This review illustrates the major pharmacological properties of this plant along with major applications of phytochemicals purified from it.

Key words: Mulberry, cancer, diabetes, deoxynojirimycin

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Antioxidative potential

Presence of wide array of phytochemicals accounts for the antioxidative potential of mulberry plant. Mulberry fruits are considered as nutritious food with many flavonoids and polyphenols and the important ones identified are apigenin, luteolin, quercetin, morin, caffeic acid, gallic acid, rutin, umbelliferone, chlorogenic acid and kaempferol[5-8]. The twigs and root bark are also rich source of phenolic compounds such as maclurin, rutin, isoquercitin, resveratrol and morin[9]. Mulberry fruit contains essential fatty acids like palmitic, oleic and linoleic acids which are important for cell membrane formation, proper development and functioning of nervous system, production of eicosanoids and many inflammatory responses[10]. Phytochemical investigation of the stem bark of M. cathayana led to the isolation and identification of cathayanin and various cathayananos[11]. Few arylbenzofuranos with antioxidant and anti-inflammatory activities were reported form M. wittiorum[10]. HPLC coupled with UV absorption detection lead to the identification of five important stilbene glycosides from M. alba[11]. Benzokuwanon E, hydroxymorusin, dicyclokuwanon EA, and
dicyclokuwanon EB are the important flavonoids isolated from M. australis and their structures were elucidated on the basis of UV, IR, MS, NMR, and CD spectral data[12]. The water extract of mulberry leaf prepared at high temperature contain four important flavonols, quercetin-3,2,6-N-glucosyl-3-0-glucose-6?-acetate, rutin and quercetin[13]. Morusulusenoic acid A, morusulusenoic acid B and moruslanosteryl acetate are the important luteol type pentacyclic triterpenoids separated from the stem bark of M. alba[14]. Moran 20K is a glycoprotein purified from the aqueous methanolic extract of the root bark of M. alba which is having antioxidative antidiabetic activity[15]. 1-deoxynojirimycin (DNJ), resveratrol, oxyresveratrol, cyanidin-3-O-beta-galactoside (Cy-3-glu), cyanidin-3-O-beta-rutinoside (Cy-3-rut), and rutin were also reported in different species of mulberry[16]. Sanggenol, kuwanon, moracin, mulberrofuran, mulberroside, 1-deoxynojirimycin, 2-O-alpha-D-galactopyranosyl-1-deoxynojirimycin, fagomine, betulinic acid, ursoic acid and beta-siosterol are the important chemical constituents of the root bark of M. atropurpurea[17]. The major pharmacologically important compounds from M. alba and other species of mulberry has been reviewed previously[18, 19].

Antidiabetic effects

Diabetes mellitus (characterized by sustained hyperglycemia), the most common metabolic disorder in humans, is associated with many secondary complications such as formation of free radicals and non enzymatic glycosylated end products. This creates very high oxidative stress and vascular complications[20, 21]. The leaves of mulberry are one of the important herbal medicines used for the treatment of hyperglycemia. It was proved by experiments in animal models that mulberry leaf extract possess antiangiogenic, antidiabetic and antiinfection activities[22]. It is effective in modulating the nitric oxide synthesis expression in the hypothalamus of streptozotocin treated rats[23]. 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[24]. 1-Deoxynojirimycin (DNJ), a known antidiabetic principle from mulberry has been shown to inhibit intestinal alpha-glucosidases resulting in reduction of blood glucose[25]. Also a hybrid of DNJ and a polysaccharide helps in regulating the expression of the hepatic gluconeogenic enzymes, glucokinase, PEP carboxykinase and glucose 6-phosphatase. The polysaccharide in this mixture is able to protect pancreatic islets from alloxan induce damage, repair the destroyed pancreatic islets, upregulate the PDX-1, insulin-1 and insulin-2 expression in pancreas and normal secretion of insulin in serum[26]. Fagomine, one of the components present in mulberry leaves is capable of inducing insulin secretion in isolated rat islet cells[27]. In patients with type 2 diabetes, mulberry treatment caused an improvement in glycemic control and fall in blood cholesterol levels enabling their use in traditional Chinese herbal and

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and RBC membrane[28, 29]. Moracin M, steppogenin-4’-O-B-D-glucoside and mulberriesoside A were also isolated from the root bark of M. alba and all the three flavonoids showed hypoglycemic effect in alloxan induced diabetic mice[29]. Retardation of starch digestion by inhibition of α-amylase, the key enzyme catalyzes the initial step in the hydrolysis of starch to smaller oligosaccharides plays a key role in the control of diabetes. M. alba leaf extract rich in tannins, flavonoids, cardiac glycosides and saponins exhibit significant α-amylase inhibitory activity[30].

Insulin resistance and low grade chronic inflammatory status will lead to the development of cardiovascular diseases and type 2 diabetes. Type 2 diabetic related insulin resistance depends both on glucose metabolism and fatty acid metabolism[31]. Improvement in insulin resistance has been suggested as an effective way to prevent life style related type 2 diabetes and vascular complications. Repeated ingestion of M. alba leaf extract reduces the insulin resistance in high fat fed KK-Ay mice[32]. Long term supplementation of mulberry leaf extract improved the markers of inflammation and insulin resistance in experimental animal models. The circulating oxidized LDL was also improved in the treated group, which is often elevated in type 2 diabetes[33]. M. alba leaf extract increases the rate of glucose uptake by a direct enhancement of insulin independent glucose transport in skeletal muscle. 5’-AMP-activated protein kinase (AMPK) is the major signaling intermediary in the exercise-stimulated insulin independent glucose transport in skeletal muscle[34]. Skeletal muscle AMPK is also implicated in a variety of antidiabetic properties of exercise, including glucose transporter 4 (GLUT4) expression, glycogen regulation, fatty acid oxidation and enhanced insulin sensitivity. Mulberry leaf extract increases the activity of both AMPK α1 and 2 in skeletal muscles and is associated with insulin independent glucose transport without change in the energy status of the muscle and reduces the risk of type 2 diabetes[35]. Decrease in adipogenesis lead to limited storage sites for free fatty acids cause increase in plasma free fatty acids. This increase in circulating free fatty acids result in fat deposition in muscle and liver causing insulin resistance and type 2 diabetes mellitus. Adiponectin is a member of the adipokine family is induced during adipocyte differentiation. Circulating levels of adiponectin will be low in patients having obesity and type 2 diabetes[36]. M. alba leaf extract stimulates differentiation of 3T3-L1 preadipocytes into adipocytes by increasing the expression of adipogenic genes and improve the secretion of adiponectin and insulin sensitivity. This mechanism of action is similar to that of the thiazolidinediones, a class of insulin sensitizing drugs used to treat type 2 diabetes[37].

**Against cardiovascular diseases**

M. alba (mulberry) has been widely used to prevent and treat symptoms associated with cardiovascular disease for over a millennium in eastern countries. Water preparations of this plant were used in the herbal prescriptions by Chinese people to reduce blood pressure. The leaf extract shown to reduce hypertension in rodents and decreases serum cholesterol and prevent atherosclerosis[38, 39]. The ethyl acetate extract of M. alba has dual vasoactive effects. The relaxation was mediated by inhibition of voltage- and receptor-dependent Ca2+ channels in vascular smooth muscle cells, while the contraction occurred via activation of ryanodine receptors in the sarcoplasmic reticulum[40]. DNA micro array analysis were used to investigate gene expression in the livers of hyperglycemic-rats treated with mulberry leaves to elucidate the mechanism behind the lipid lowering effect of mulberry. Dietary supplementation increased protein expression of CPT1A, ACOX2, PHYH and the activity of acyl-CoA oxidase/dehydrogenase, the rate limiting enzymes of fatty acid oxidation. The genes upregulated by mulberry included the following PPAR γ and or PPAR δ targets and many of them are involved in fatty acid oxidation. Mulberry induced downregulation of AngII results in the activation of lipoprotein lipase and enhanced triglyceride hydrolysis. Mulberry administration also upregulated the Gyk gene and caused a reduction in the plasma non esterified fatty acid level. Scd is the gene involved in lipogenesis and this gene was downregulated after treatment with mulberry which inhibits lipogenesis and facilitates fatty acid oxidation[41]. M. bombycis root extract exhibited strong anti-lipase activity, with an IC50 value of 2.07 µg/ml in fully differentiated 3T3-L1 adipocytes and adipose tissues. The extract increased lipolytic effects such as decreased intracellular triglyceride and the release of glycerol. Moreover it inhibited phosphodiesterase activity in a dose dependent manner[42]. So it does have pharmacological applications in metabolic disorders such as obesity. DNJ present in mulberry leaf extract helps in increasing serum adiponectin level, stimulated AMP activated protein kinase to activate β-oxidation which inhibit lipid accumulation in liver[43]. Mulberry water extract inhibited acetyl coenzyme A carboxylase activities by stimulating AMPK and attenuated the expression of sterol regulatory element binding protein 1 and its target molecules such as fatty acid synthase. In contrast, the lipolytic enzyme expressions of PPAR gamma and carnitine palmitoyltransferase 1 were increased[44].

12 weeks continuous supplementation of DNJ rich mulberry leaf extract capsule for humans showed a modest decrease in serum triglyceride levels and beneficial changes in lipid profile without any side effects[45]. Administration of freeze dried powder of M. alba fruits to rats resulted in a significant decrease in serum and liver triglyceride, total cholesterol, serum LDL and decrease in atherogenic index. Also an increase in serum HDL level, RBC and liver SOD level and blood glutathione peroxidase level was observed. The serum and liver thiobarbituric acid content was reduced indicating the low level of lipid peroxidation[46]. Mulberry leaf powder can preserve the cardiac function in experimental autoimmune myocarditis by modulating oxidative stress induced MAPK activation and further afford protection against endoplasmic reticulum stress mediated apoptosis. It significantly decreased oxidative stress, myocyte apoptosis, cellular infiltration, cardiac fibrosis, mass cell density, myocardial levels of sarco/endoplasmic reticulum Ca2+ ATPase2, p22phox, receptor for advanced glycation end products, phospho-p38 mitogen activated protein kinase, phospho-c-Jun-NH2-terminal protein kinase, glucose regulated protein78, caspase12 and osteopontin levels[47]. Morusinol extracted from M. alba root bark significantly inhibited collagen and arachidonic acid induced platelet aggregation and TXB2 formation in cultured platelets. So it is effective in inhibiting arterial thrombosis in vivo due to antiplatelet activity and exerts beneficial effects on transient ischemic attacks or stroke via modulation of platelet activation[48]. Some isoprenylated flavonoids with adipogenesis promoting activity were purified from M. nigra and M. notabilis[49, 50]. M. alba leaf extract increases the vascular smooth muscle cell migration in a dose dependent manner by inhibiting the activities of MMP-2 and 9, phosphorylation of PAK, protein expression of small GTPases (c-Raf, Ras, Rac1, Cdc42, and RhoA) and NF-kappaB expression[51]. Also the leaf extract helps in inhibiting the vascular smooth muscle proliferation by the upregulation of p53 and inhibition of cyclin dependent kinase[52].

**Anticancer effects**

Cancer is a serious public health problem world wide. Most of the natural compounds targets inflammatory pathways and immune modulation for the prevention and treatment of cancer. 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[53]. 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[54]. Albanol A isolated from the root bark of M. alba induced potent cytotoxicity (IC50 1.7mM) in HL60 cells by inhibiting topoisomerase II activity (IC50 22.8mM). In addition, it induced early apoptosis through cell death receptor pathway and mitochondrial pathway, observed by membrane phospholipid exposure, reduced levels of pro caspase3, 8 and 9 and increased levels of cleaved caspase 3, 8 and 9 and increased bax/Bcl2 ratio[55]. The anticancer activity of the essential oil separated from M. rotundifolia Koidz was studied in human larynx epidermoid carcinoma (HeP2) and human colon adenocarcinoma (SW620) cell lines with African green monkey kidney (Vero) cell line as a control. The oil at 0.1 -100 µg/ml had no effect on Vero cell viability. The median lethal concentration (LC50) of the oil on the cytotoxicity of Hep2, SW620 and Vero were 70, 120 and 280 µg/ml respectively[56]. Resveratrol, purified from the methanol extract of M. alba showed heparinase inhibition and antimetastatic effects on murine B16 melanoma cells[57]. M. alba is a rich source of prenylated cyto-
toxic flavonoids such as sanguenon J and K, cyclomorusin, morusin, atalantoflavone, kaempferol etc. Morusin is the most potent among them with an IC_{50} value of 0.64 µM against HeLa cells[58]. 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[59, 60]. A new galactose binding lectin was also purified from M. alba leaves with cytotoxic activity on human breast cancer (IC_{50}=8.5 µg) and colon cancer cells (IC_{50}=16 µg)[61].

Anticytokines are a group of phenolic compounds with beneficial effects in reducing the risk of cardiovascular diseases and cancer because of its antioxidant, anti-inflammatory and chemopreventive properties[62]. Cyanidin-3-rutinoside and cyanidin-3-glucoside are the two anthocyanins present in mulberry which have strong antioxidant properties. They have shown to be inhibiting the invasion and migration of human lung cancer A549 cells by downregulating the expression of MMP-2 and urokinase plasminogen activator and enhances the expression of TIMP-2 and plasminogen activator inhibitor. Also an inhibition of the activation of NF-kappa B and c-jun was also observed in this case[63]. Osajin is a prenylated isoflavone isolated from the fruit of Maclura pomifera, a tree belonging to the mulberry family. It exerts multiple effects such as loss of mitochondrial transmembrane potential, release of cytochrome C, expression of Fas ligand, suppression of glucose regulated protein 78 and activation of various caspases and proapoptotic proteins in human nasopharyngeal carcinoma cells. So osajin induced apoptosis include extrinsic death receptor pathway and intrinsic pathways relying on mitochondria and endoplasmic reticulum[64]. Chalcones, a group of aromatic enones from plants, form the central core of a number of biologically important compounds. Investigation on ethanol extract of the leaves of M. alba L. yielded two new chalcone derivatives, morachalcone B and C with potent cytotoxic effects[65]. Flavonoids such as sanggenol L, sanggenol M and different types of mulberryflavonoids with cytotoxic effects were also purified from M. mongolica[66].

Anti-inflammatory effects
Mulberry plants have a long history in traditional medicine as anti-inflammatory agents. The root epidermis of M. alba shown to have anti-inflammatory effects[67]. Butanol extract of M. alba significantly reduced LPS-induced PGE2 production, TNF-alpha and COX-2 expression in RAW264.7 macrophages[68]. Methanol extract of M. alba contains compounds with inducible nitric oxide synthase (iNOS) inhibitory activity which can contribute to its anti-inflammatory properties[69]. It exerts antiasthmatic effect in experimental mouse model via enhancement of CD4 CD25 Foxp3 regulatory T cells and inhibition of Th2 cytokines[70]. The extract of M. bombycis has anti-inflammatory and inhibitory effect on collagen induced arthritis. It acts by decreasing the infiltration of immune cells, synovial hyperplasia, cartilage destruction and bone erosion. The mRNA levels of MMP1/3, inflammatory cytokines and chemokines were significantly suppressed, number of osteoclasts were reduced and activation of NF-kappaB and Ap-1 were observed on treatment with the extract[71]. M. nigra leaf extract and M. Ihou Koidz fruit extract are capable of reducing the carrageenan-induced paw edema as well as fibrovascular tissue growth induced by s.c. cotton pellet implantation in animal models indicating its anti-inflammatory property[72, 73].

Cudraflavone B is a prenylated flavonoid found in large amounts in the roots of M. alba causes a significant inhibition of inflammatory mediators in selected in vitro models. It was a potent inhibitor of TNFα by blocking the translocation of NF-kB from the cytoplasm to the nucleus. The NF-kB activity reduction resulted in the inhibition of cyclooxygenase 2 (COX-2) gene expression also[74]. The anti-inflammatory compound wittifuran I was purified from the ethanolic extract of stem bark of M. wittiorum[66]. Another compound resveratrol from M. alba inhibits IL-8 secretion by blocking MAPK phosphorylation and NF-kappaB activation in LPS induced human monocyctic cell line THP-1[75]. Sanguenon C and O, two Diels-Alder type adducts isolated from M. alba, inhibit NO production through the iNOS induction and activation of nuclear factor (NF-kB) in LPS-induced RAW264.7 cells indicating its anti-inflammatory potential[66]. Several arybenzofurans (moracins and mulberrofuran of different types), prenylated flavonoids (kuwanons, morusin, sangegon F, betulinic acid etc.) from M. alba var. maculalis Perro showed significant inhibitory activity towards the differentiation of 3T3-L1 adipocytes and inhibition in NO production in RAW264.7 cells[77]. Phytochemical fractionation of the methanol extract of M. alba root bark lead to the identification of two chalcone derived Diels Alder adducts, kuwanon J thymelylester and kuwanon R with inhibitory effect on NFkB with IC_{50} value of 4.65 and 7.38 µM respectively[59]. Inhibitors of phosphodiesterase -4 (PDE4) enzymes have therapeutic applications as anti-inflammatory agent because inhibition of PDE-4 will lead to the accumulation of cAMP and thus attenuated inflammatory responses in various cell types. Molecular docking studies have shown that moracin M from M. alba can inhibit the activity of a variety of PDE-4 enzymes[79].

Against neurological disorders
Unlike beneficial effect of mulberry in treating diabetes, cardiovascular disease, cancer etc., but its effects on neurological disorders are less studied. The neurotoxicity in Alzheimers disease (AD) is associated with the accumulation of amyloid beta-peptides that forms as a plaque in brain. The methanol extract of mulberry leaves contain compounds such kaempferol -3-O-glucoside, and kaempferol -3-O-(6-malonyl) glucoside which inhibits the formation of amyloid beta-peptide fibrils in vitro, and protects hippocampal neurons from amyloid beta-peptide induced cell death[68, 81]. The amyloid plaques are formed by the proteolysis of amyloid precursor protein by the β, δ or βδ secretase enzyme. Therapeutic efforts to target AD have now focused on the disruption of this cascade by blocking these enzymes. Many flavones are identified from M. ihou with δ-secretase inhibitory activity[72]. Cholinesterases are key enzymes that play important roles in cholinergic transmission. Eight flavonoids including kuwanon U, kuwanon E, kuwanon C morusin, morusinol displaying cholinesterase inhibitory (both acetylcholine and butyrylcholine esterase) activity were isolated from the root bark of M. ihou L.[83]. The neuroprotective effect of oxyresveratrol was studied in vitro model of stretch-induced trauma in co-cultures of neurons and glia, or by exposing cultures to high levels of glutamate. Trauma produced marked neuronal death and oxyresveratrol significantly inhibited this death. Microscopic examination of glia suggested signs of toxicity in cultures treated with 100 µM oxyresveratrol, as demonstrated by elevated S-100B protein release and a high proportion of cells with condensed nuclei. Cultures exposed to glutamate for 24 h exhibited ~ 37% neuronal loss, which was not inhibited by oxyresveratrol[84]. Studies have demonstrated the beneficial effects of mulberry on the induction of an antioxidant defense system and improvement of memory deterioration in ageing animals[85]. The neuroprotective effect of cyanidine-3-glucoside (C3G) fraction from M. alba was studied in oxygen deprivation and glutamate induced cell death in rat primary cortical neurons. C3G did not provide a protective effect against glutamate induced cell death, but provide protection against oxygen deprived cell death by maintaining the mitochondrial membrane potential[86].

Against skin diseases
Melanin present in the skin protects from UV induced hyper pigmentation, wrinkling, melasma and cancer. Tyrosinase is an important enzyme in melanin production and in mammals the skin pigmentation results from the transfer of melanosomes from melanocytes to keratinocytes in the epidermis. M. alba L. leaf extract exhibited potent inhibitory effects on mushroom tyrosinase, mammalian tyrosinase, and melanin synthesis in Melan-a cells[87], TMBC, a chalcone from the stem of M. nigra modulated melanogenesis by inhibiting tyrosinase. It inhibited the L-dopa oxidase activity of mushroom tyrosinase which was more potent than kojic acid a well-known tyrosinase inhibitor[88]. Topical applications of mulberroside A, oxyresveratrol, and oxyresveratrol-3-O-glucoside clearly caused depigmentation, reduced melanin indices, inhibited tyrosinase activity, and decreased melanin content in UV induced hyperpigmentation in guinea pig skin. Oxyresveratrol and oxyresveratrol-3-O-glucoside more potently inhibited melanogenesis than mulberroside A. This treatment decreased the expression of MITF gene, that are regulating the transcription of proteins involved in melanocyte pigmentation[89].

Figure 1. Structure of some pharmacologically important compounds isolated from mulberry

1-Deoxynojirimycin

Resveratrol

Oxyresveratrol

Rutin

Kuwanon G

Moracin U

Moracin M

Moracin S
Against liver and gastrointestinal diseases

The chemical investigation of the twigs of M. mesozygia resulted in the isolation of several compounds and few of them exhibited hepatoprotective activities\(^9\). A glycoprotein (MIL) purified from M. indica protects against CCl\(_4\)-induced liver damage. MIL significantly reduced the activity of alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and thiobarbituric acid-reactive substances (TBARS) in CCl\(_4\)-treated mice. It reduced the activity of COX-2 and expression of TNF-α and IL-1 beta in liver from CCl\(_4\)-treated mice. Moreover, supplementation of MIL suppressed stress-activated protein kinase/c-jun N-terminal kinase phosphorylation and activator protein-1 transcriptional activation in livers of CCl\(_4\)-treated mice\(^{9,10}\). M. alba extract significantly reduced the gastric mucosal injury in experimental rats induced by tween 20 and absolute ethanol with marked reduction in the leucocytes infiltration to submucosal layer\(^{9,11}\).

Antimicrobial activities

The methanolic extract of the bark of M. mesozygia as well as its constituents (cycloartocarpius and different types of moracin) are used for the treatment of infections associated with microorganisms\(^{9,12}\). Prenylated flavonoids isolated from M. alba showed antibacterial, antifungal and antiviral activities\(^{9,13}\). Kuwanon G was isolated from the ethyl acetate fraction of methanolic extract of M. alba is acting as an antibacterial agent against oral pathogens\(^{9,14}\). Chalcomoracin, a leaf phytoalexine of mulberry tree exhibited considerable antibacterial activity against methicillin-resistant Staphylococcus aureus\(^{9,15}\).

CONCLUSIONS

Mulberry is the one among the most studied plants for pharmacological potential. Research over the years elucidated the existence of a number of active molecules in it. The mechanism included in the exciting pharmacological effect has been studied with a significant number of compounds purified from mulberry. The synthetic analogues of the purified compounds, also shown to be effective in the treatment of various diseases. More detailed studies in future with the natural vs. synthetic compounds will clearly show the potential of these compounds in the therapeutic field. It is expected that in the 21\(^{st}\) century more research will be focused on the natural source based compounds to treat various diseases and mulberry is definitely be one of the species to be explored more extensively.

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