Mulberry as a Life Savior - A Review

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Abstract
Plants play an important role in well-being of human beings and have been witnessed by their presence in the Rigveda and Ayurveda. Among those plants, Morus spp. is the one having versatile nature because of the presence of numerous phytochemicals in its different parts and also termed as ‘Kalpavrishka’. Mulberry (Morus spp.) belongs to family Moraceae and is widely planted in Asia. Although Morus spp. are the primary food of silkworm, Bombyx mori L. widely grown for rearing of silkworm. A wide range of the phytochemicals present in the leaves, fruit, root and wood of Morus because of which they possess wide range of biological functions (Antioxidant, anti-diabetic, anti-obesity, anticancer, antibacterial, antiviral, crypto protective and neuroprotective activities etc.). This review reveals the wide range of important life savior pharmacological properties of mulberry plant.

Keywords: Mulberry, Phytochemicals, Pharmacological properties, Morus spp., Biological functions

Introduction
Medicinal plants play an important role in Indian Ayurveda system of medicine and many active compounds were isolated from the plants by researchers which used as medicines. These active compounds are chemically in nature which is known as phyto-chemicals or secondary plant products. Mulberry plant is one of conventional herbs which are used in medicine from centuries ago due to its chemical composition and pharmacological functions [9]. Mulberry is a fast growing woody perennial plant belongs to the family Moraceae and the genus Morus that contains more than 15 species of deciduous plants. The major ones include Morus Alba, Morus indica, Morus nigra, Morus rubra, Morus australis, Morus atropurpurea, Morus cathayana, Morus notabilis and Morus mesozygia [56]. Mulberry is found in a wide range of climatic, topographical and soil conditions, and it is widely distributed, from temperate to subtropical regions of the Northern hemisphere to the tropics of the Southern hemisphere. Since the ancient Chinese ‘Material Medica’ describes many medicinal benefits of mulberry, the potential nutritional and medicinal values of mulberry have attracted increasing research interest. Recent studies have demonstrated the nutritional value and health benefits associated with mulberry consumption [73].

Mulberry foliage is valued as the primary food for silkworms, supporting the silk industry for centuries [29]. The silkworm eats only mulberry leaves to make its cocoon, through which silk is produced, and there is a high correlation between the leaf protein content and the efficiency of cocoon production [65]. Various amino acids like threonine, valine, methionine, leucine, phenylalanine, lysine, histidine, and arginine found in mulberry leaves that are needed for silkworm growth. It is well established that the growth of silkworms, cocoon production and raw silk quality depends on the quality of mulberry leaves, which in turn is closely related to the plant varieties, environmental conditions, and cultivation practice [42]. Being nutritious, palatable, non-toxic and due to its ability to improve milk production can be used as fodder to dairy animals [9]. The high crude protein content and organic matter digestibility of mulberry leaves are superior to most tropical grasses commonly used as cattle feed [79]. In Traditional Chinese Medicine (TCM), leaves, fruits, and bark of M. Alba have long been used to treat fever, protect liver damage, improve eyesight, strengthen joints, facilitate discharge of urine, and lower blood pressure [9]. In Korea and Japan, mulberry leaves consume as an anti-hyperglycemic supplement to diabetic patients [34]. Mulberry leaves are effective against high blood pressure and hangover from alcohol [49]. In East and Southeast Asia, the drinking of mulberry tea is gaining popularity. The tea is rich in γ-aminobutyric acid (2.7 mg·g^-1 dry weight) which is 10 times higher than that of green tea [66]. In Turkey and Greece, trees of M. Alba are grown for fruits rather than foliage [22]. The fruits are used to produce mulberry juice, jam, liquor, and canned mulberries. In China, the leaves of M. Alba are processed into tea while fruit juice is consumed as a health beverage [29]. Mulberry can be also use in mushroom Production [45]. In India, mulberry wood is made into sports equipment, furniture, household
utensils, and agricultural implements [16].

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 [64]. Mulberry leaves containing sugars, rutin, quercetin, volatile oil, amino acid, vitamins and microelements that have so many pharmacological activities such as reducing blood glucose, ant hyperlipidemia, hypertensive, bacteriostatic and antivirus. Bioactive compounds in different species of mulberry can enhance lifespan [69]. Different pharmaceutical properties of mulberry plants are reviewed by many scientists and they have reported that, many biochemical compounds such as Moron line, Alba funan, Albanol, Morusin, Kuwanol, Calystegine and Hydroxymorcin are isolated from mulberry leaves play an important role in pharmaceutical industry [9].

Photochemical studies have identified three flavonol glycosides, quercetin 3-(6 malonylg glucoside), rutin and isoquercitrin, as major antioxidant compounds in the ethanol leaf extract of M. Alba [44] whereas by butanol extraction of leaf, two novel prenyllavannes and a glycoside, along with six known compounds, isoquercitrin, astragalin, scopolin, skimming, roseoids II and benzyl D-glucopyranoside were isolated [18]. Phytochemical studies of fruits of Morus Alba revealed that there are five anthocyanins [20] and 25 phenolic compounds [71] present in the fruit. From the root bark of M. Alba, polyhydroxylated alkaloids have been isolated, including 1-deoxyojirimycin (DNJ) and its derivatives [7]. The contents of DNJ is also present in the leaves of some varieties of mulberry, usually the younger leaves have higher DNJ content than the older leaves [27]. Other compounds identified from the root and root bark include terpenoids, flavonoids, stilbenoids and coumarins. Some bioactive compounds include mulberroside, resveratrol and oxyresveratrol found in twig and stem of M. Alba [14].

Antioxidant activities of mulberry

Free radicals are chemical species possessing an unpaired electron as a result of the loss of 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 [2]. The potentially reactive derivatives of oxygen, ascribed as Reactive Oxygen Species (ROS) such as superoxide radical (O^{-2}), hydrogen peroxide (H_{2}O_{2}), hydroxy radicals (OH) and alkoxyl radicals (RO) are routinely generated at low levels by plant cells. 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 [21]. However, exposure of plants to adverse environmental conditions, ROS production will overcome scavenging systems favoring the ROS upsurge that culminate in oxidative stress [64]. 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 [63]. To avoid hazards associated with oxidative stress, antioxidants in the form of food supplement is required by the human body [56].

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 [31]. Four flavonoids were isolated and all these compounds showed DPPH and ABTS radical scavenging activity [74]. Antioxidant potential of fruits of four mulberry species namely Morus 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 [30]. White mulberry stem bark, root bark, leaves and fruit content of methanolic extract was evaluated by in vitro standard method using spectrophotometer [37]. Among the extracts, stem bark showed highest antioxidant activity and hence, plant could serve as effective free radical inhibitor. Mulberry leaves treated with UV-C found to contain three different phytalexins namely moracin C, moracin N and chalconomarin and they are capable of scavenging superoxide anion [60]. Three different extracts of M. 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 biomembranes and biomolecules [43].

Hypoglycemic activity

Hypoglycemia is a condition that occurs when blood sugar level is too low in body. Diabetes mellitus is caused by the ineffectiveness of the insulin produced by pancreas [10]. The Diabetes mellitus is a group of metabolic disorders. It is characterized by high blood sugar (glucose) levels. This high blood sugar (glucose) levels is in response to the defects in insulin secretion, or its action, or both. The disease diabetes mellitus was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Increased levels of blood glucose (which may also called as hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine [32]. Due to inadequacy of insulin secreted by pancreas the concentration level of glucose increase in blood which harm many body systems in specifically the blood vessels and nerves [10].

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 antihyperglycemic, antioxidant and antiglycation activities [48]. It is effective in modulating the nitric oxide synthase expression in the hypothalamus of streptozotocin treated rats [52], 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 [59]. 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 [34]. 1- Deoxyojirimycin (DNJ), a known antidiabetic principle from mulberry has been shown to inhibit intestinal α-glucosidases resulting in reduction of blood glucose [28]. Fagomine, one of the components present in mulberry leaves is capable of inducing insulin secretion in isolated rat islet cells [67]. Moracin M, steppogenin-4'-O-B-D glucoside and mulberroside A were also isolated from the root bark of M. Alba and all the three flavones showed hypoglycemic effect in alloxan induced diabetic mice [74]. The extracts from the root bark of mulberry tree contains some
components which showed hypoglycemic function, had defensive consequences on pancreatic β cells, obstruct their degeneration and decreased lipid peroxidation [10].

Anti-obesity activity
Obesity is defined as abnormal or extravagant fat accumulation that extant a risk to health. An obese person has accumulated so much body fat that it might have a negative effect on their health. Obesity is related with the diabetes, hypercholesterolemia, hyperlipidemia, hepatic steatosis, and atherosclerosis and decrease the amount of sugars absorbed has consequences for body weight [10]. Researchers suggested that mulberry extract might be beneficial in preventing human diabetes by suppressing intestinal alpha-glucosidase activities [8]. 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. 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 anti-obesity action on diet-induced mice [10]. Quercetin, the quantitatively major flavonoids glycoside in mulberry leaves effectively suppressed the blood glucose levels [34]. Daily consumption of mulberry leaves improved hyperglycemia in diabetic rats and reduced oxidative stress in liver [39].

Hyperlipidemia activity
Hyperlipidemia is a characterized by excess cholesterol and fatty substances in the blood. Hyperlipidemia is a risk factor for heart disease. Diabetes mellitus is related with different kinds of lipid peculiarity. The lipaemia, cholesterol, especially LDL (low-density lipoprotein) and VLDL (Very-low-density lipoprotein) cholesterol are engaged in the growth of atherosclerosis and related abnormalities [5]. Morus Alba known for its medicinal properties and traditionally used for hypolipidemic activities. Consumption of MRBF-2 fraction of M. Alba L. root bark (70% alcohol extract) may act as potent hypocholesterolemic nutrient and inhibition of LDL, anthoregenic modifications and lipid peroxidase formation in hypocholesterolemic rats. Moracin present in mulberry leaves with IC50 of 52.8 mg/mL [40]. Further evaluation and clinical trials may reveal the therapeutic potential of M. 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 M. wittiorum was extracted with 95% ethyl alcohol, flavonoids and quercetins present in the bark exhibited selective cytotoxicity against hepatoma cells in rats with an IC50 of 52.8 mg/mL [40].

Neuroprotective activity
Morus 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 [53]. Oxyreservatrol, a natural hydroxystilbene present in mulberry extracts, has been shown to have a neuroprotective effect in the case of neurodegenerative diseases due to oxidative damage such as Alzheimer’s disease which is usually marked by cellular damage by high lipid peroxidation and increase in iron and aluminum [58]. Fruit extract of M. nigra has neuroprotective effect in inhibition of oxidative stress in the zebrafish brain owing to potent antioxidant properties of mulberry [23]. 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 [12]. 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 [33]. Studies have demonstrated the beneficial effects of mulberry on the induction of an antioxidant defense system and improvement of memory deterioration in ageing animals [62]. The beneficial effect of mulberry extract (ME) rich in dependent manner [15] & [46]. Phenolic compounds from mulberry, M. Alba (L.) induces in vitro anticancer activity in hepatoma cells by cell cycle arrest at G2-M phase and inhibition of topo-isomerase II activity [49]. A new galactose binding lectin was also purified from M. Alba leaves with cytotoxic activity on human breast cancer (IC50 8.5 µg) and colon cancer cells (IC50 16 µg) [17]. The anthocyanins 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 [49]. 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 [73]. Between the high content of anthocyanins, vitamin C, vitamin A, and various other polyphenolic and phytonutrient compounds, mulberries are absolutely packed with antioxidants. Antioxidants are the main line of defense against free radicals, which form a dangerous by-product of cellular metabolism and can damage healthy cells, causing them to mutate into cancerous ones. The diverse range of antioxidants found in mulberries means that they can neutralize these free radicals quickly before too much damage is done [32]. Prenylated flavanone, 7, 2', 4', 6'-tetrahydroyx-6-geryl flavanone separated from ethyl acetate extract of Morus Alba root showed cytotoxic activity against hepatoma cells in rats with an IC50 of 52.8 mg/mL [40]. Further evaluation and clinical trials may reveal the therapeutic potential of M. 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 M. 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 [68].
phenolics and anthocyanins were evaluated. Six month old senescent- accelerated mice [SAMP8] and [SAMRI] were fed a basal diet supplement with 0.18 and 0.9 per cent 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 [75]. 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 [11]. 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 butryrylcholine esterase) activity were isolated from the root bark of M. lhou L. [38].

Against gastrointestinal disorders
Mulberries are filled with nutrients that are important for our body, including iron, riboflavin, vitamin C, vitamin K, potassium, phosphorous, and calcium. They also contain a significant amount of dietary fiber and a wide range of organic compounds, including phytonutrients, zeaxanthin, resveratrol, anthocyanins, lutein, and various polyphenolic compounds. Dietary fiber can help to improve digestion by bulking up the stool, thereby speeding up the movement of food through the digestive tract, while also reducing occurrences of constipation, bloating, and cramping [32]. 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 [1]. The oral administration of methanolic extract from M. nigra fruits at a high dose (300 mg/kg) can protect gastric mucosa against acidified ethanol-induced acute gastric ulcer in female mice [50]. The mulberry consumption effectively prevents constipation in mice and is a promising therapeutic candidate for constipation. They also reported that mulberry treatment also increased the concentration of acetic, propionic, butyric valeric and isovaleric acids, increased the abundance of lactobacillus and bifidobacterium in faeces and decrease the abundance of helicobacter and prevotellaceae in faeces [28].

Antimicrobial activities
Infectious diseases accounts for high proportion of health problems in the world. Microorganisms have developed resistance to many antibiotics and as a result, immense clinical problems in the treatment of infectious diseases have been created. To solve this, researchers had identified many antimicrobial substances from medicinal plants including mulberry. The ethanolic extract of Morus indica leaf has antibacterial activity against Staphylococcus aureus and methanolic extract of M. indica leaf has antifungal activity against Aspergillus niger and Penicillium [51]. The methanolic extract of the bark of M. mesoyxia as well as its constituents (cyclotocecarpin and different types of moracins) are used for the treatment of infections associated with microorganisms [41]. Kuwanon G isolated from the methanol root bark extract of M. Alba has been reported to exhibit antibacterial activity against oral pathogens such as Streptococcus mutans, Streptococcus sanguis, Streptococcus sobrinus, and Porphyromonas gingivalis, with the minimum inhibitory concentration (MIC) of 8 µg·mL-1 [54]. Prenylated flavonoids isolated from M. Alba showed antibacterial, antifungal and antiviral activities [20]. Flavonoids isolated from root bark of M. Alba viz., leachianone G and mulberroside C show potent antiviral activity (IC50 1.6 mg.Ml-1) and weak activity (IC50 75 mg. MI-1) against herpes simplex type 1 virus (HSV-1). Chalcromarin, a leaf phytalexine of mulberry tree exhibited considerable antibacterial activity against meticillin-resistant Staphylococcus aureus [28].

Against skin diseases
Melanin is a complex polymer derived from the amino acid tyrosine. Melanin is responsible for determining skin color. Melanin is produced through a multistage chemical process known as melanogenesis, where the oxidation of amino acid tyrosine is followed by polymerization. The melanin pigments are produced in specialized group of cells known as melanocytes. Tyrosinase is a copper- containing enzyme present in plant and animal tissues that catalyzes the production of melanin and other pigments from tyrosine by oxidation. It is found inside melanosomes which are synthesized in the skin melanocytes. In humans, the tyrosine enzyme is encoded by the TYR gene. Tyrosinase inhibitors are more important in improving skin to prevent the overproduction of melanin [13]. Melanin protects from UV induced hyper pigmentation, wrinkling, melasma (Brown patches on skin) and cancer [50]. A number of natural tyrosinase inhibitors have been reported [36]. Among those, extracts from leaves and root barks of mulberry exhibited high inhibition on the DOPA oxidase activity and anti-tyrosinase activity [44]. Mulberroside F isolated from the methanol leaf extract of M. Alba exhibits anti-tyrosinase activity that is 4.5-fold stronger than kojic acid and has an inhibitory effect on melanin formation in melan-a cells (44). Oxyresveratrol exhibits an inhibitory activity that is 32-fold stronger than kojic acid [61]. M. Alba L. leaf extract exhibited potent inhibitory effects on mushroom tyrosinase, mammalian tyrosinase, and melanin synthesis in Melan-a cells [44]. The extract of mulberry (M. Alba) from leaves or root barks exhibited free radical scavenging and antioxidant activities thus, it may benefit for depigmentation [4]. TMBC, a chalcone from the stem of M. nigra modulated melanogenesis by inhibiting tyrosinase [76]. Topical applications of mulberroside A, oxyresveratrol, and oxyresveratrol-3-O-glucoside clearly caused de-pigmentation, 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 [55]. Mulberroside F isolated from mulberry leaves might be used as a skin whitening agent [13]. Mulberries also boast a high level of vitamin A and vitamin E, along with a range of carotenoid components like lutein, beta-carotene, zeaxanthin, and alphacarotene. All of these elements act as antioxidants that specifically affect the skin, tissue, hair, and other areas of the body where free radicals strike. Mulberries can aid in skin care, reduce the appearance of blemishes and age spots, and keep hair shiny and healthy by preventing the oxidative actions of free radicals [32].
Conclusion
Mulberry being the primary food for silkworm Bombyx mori L., supported the silk industry over centuries. Mulberry plant is also considered as the important traditional herbs widely used in medicine from centuries ago. Mulberry is rich in phenols (resveratrol, oxyresveratrol, chlorogenic acid, mulberroside, maclurin and moracin), 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, anticarcinogenic, antibacterial, antiviral, anti-obesity, anti-apoptotic, anti-diabetic, neuroprotective activities. The Phytochemical composition varies with the species of Morus and the plant part used. However, human intervention studies on the pharmacological activities of mulberry fruits are limited. Therefore, future studies should explore the effect of mulberry fruit consumption on human health and elucidate the detailed compounds.

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