

Review Article**Phytochemistry and bioactivity of *Morus alba* (Mulberry) plant: A comprehensive review**

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Abstract

Morus alba have been used traditionally in a variety of ailments. Different parts of *Morus alba* show antidiabetic, antibacterial, anticancer, cardiovascular, hypolipidemic, antioxidant, antiatherogenic and anti-inflammatory activity besides having high nutritional value. It contains deoxynojirimycin a natural α glucosidase inhibitor. It also has tyrosinase inhibitory activity and acts on glucose uptake. Resveratrol an antioxidant in mulberry is effective in diabetes. Overall it can be considered a multi utility plant and can be exploited as an alternative therapy in various ailments. Several online and offline resources were utilized. The main source of data collection was articles both research and review published by reputed publishers such as Springer, Elsevier and other indexed journals. Online databases like PubMed, Research gate, Scopus and Science Direct were also referred for gathering all available data on *Morus alba*.

Keywords: *Morus alba*, Resveratrol, Deoxynojirimycin, antioxidant, antidiabetic

Introduction

Morus alba is a rapid growing, medium-sized mulberry tree up to 10–20 m tall. Originally from China now widely cultivated and naturalized worldwide. *Morus alba* has been used traditionally since long in headache, hypertension, diabetes, as diuretic, particularly, mulberry twigs were found very effective in relieving pain and numbness of joints (Choi et al., 2013). It is also an effective antipyretic, eyesight improver, hepatoprotective and joint strengthener. *Morus alba* twigs have been used in folk medicine since ages as antidiabetic, antitussive, in stroke and beriberi (Zhang et al., 2016). In present review we describe different parts of *Morus alba* plant possess different phytochemicals and pharmacological activities.

Methodology

A detailed and critical literature survey was done of available information on *Morus alba* up to December 2017. Several online and offline resources were utilized. The main source of data collection was articles both research and review published by reputed publishers such as Springer, Elsevier and other indexed journals. Online databases like PubMed, Research gate, Scopus and Science Direct were also referred for gathering all

available data on *Morus alba*. The paid articles were accessed through university library facility of Dr B. A. M. University and Ph D and dissertation thesis available in library of Y. B. Chavan College of Pharmacy were also referred. Herbarium “MACH12356” in Maulana Azad College was also used to collect data regarding the morphological and identification characteristics of the tree and expert botanist of Botony department of the same college was consulted to authenticate the identification of plant. The plant was also searched on Indian Medicinal Plant Database and Encyclopedia on Indian Medicinal Plants for ascertaining its use in Indian systems of medicine. Only data related to its phytoconstituents and pharmacological activities were sorted from comprehensive data about *Morus alba* as it a widely known and utilized plant in Indian and Chinese system of medicine.

Literature was collected using Google Scholar, PubMed and Science Direct using the following keywords: *Morus alba*, mulberry, shahtoot, phytoconstituents of *Morus alba*, pharmacological activities of *Morus alba*. This review not only highlights the phytoconstituents and activities of *Morus alba* but also explores the possibility of it being a promising nutraceutical, cosmeceutical and a novel drug.

Phytochemistry of different parts of *Morus alba* and their activities**Twig**

Photochemical studies have shown presence of terpenoids,

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alkaloids, flavonoids (including chalcones and anthocyanins) phenolic acids, stilbenoids and coumarins in *Morus alba* (Chan et al., 2016). Prenyl flavonoids, flavonoids, coumarins and stilbenes are found in twigs. Prenyl flavonoids and flavonoids in twigs are mainly effective in obesity, oxidation, aging and hepatotoxicity. Also coumarins and resveratrol derivatives in mulberry twigs have strong radical scavenging and anti-inflammatory activities. Three resveratrol derivatives, namely oxyresveratrol 3'-O- β -D-glucoside, oxyresveratrol (Figure 1), *t*-resveratrol and moracin were isolated from *Morus alba* twigs (Figure 1). Oxyresveratrol and *t*-resveratrol are majorly responsible for antioxidant and antityrosinase activity of twigs. Also isolated and identified are oxyresveratrol 3'-O- β -D-glucoside and moracin derivatives from *Morus alba* root bark and fruit. Resveratrol derivatives and moracin in *Morus alba* plant are effective in inflammation, diabetes, aging and oxidation. Specifically oxyresveratrol is a tyrosinase inhibitor and an anti-browning and skin-whitening agent used in food and cosmetics industry. *Trans*-resveratrol, a phytoalexin present naturally in many plants has many biological and pharmacological activities. 2-arylbenzofuran derivatives and moracin are potential phytochemicals effective in cancer, inflammation, hyperlipidemia and oxidation. Twigs containing resveratrol and moracin can be developed as nutraceuticals and cosmeceuticals (Choi et al., 2013). Natural tyrosinase inhibitors have limited natural sources and are in great demand in food and cosmetic industry. Twigs have not been explored as natural tyrosinase inhibitors yet and are usually rejected as agricultural waste. Phenolic compounds like oxyresveratrol, resveratrol, moracin M, maclurin, rutin, isoquercitrin and morin from mulberry twigs and morin are potential antioxidants and tyrosinase inhibitors and can be exploited accordingly (Chang et al., 2001). *Morus* plant young twig extract has shown potent inhibitory effects on human tyrosinase and melanin synthesis in B-16 melanoma cells. Also *Morus alba* twig extract and oxyresveratrol show notable antibrowning effects on cloudy apple juices and fresh-cut apples slices with ascorbic acid (Cheng et al., 2007). From seventeen compounds identified are five flavones, four benzofurans, three flavanones, two chalcones, two phenolic acids and one stilbene derivative. 5,7,20,40-tetrahydroxy-3-methoxyflavone and eriodictyol (Figure 1) and steppogenin 2,4,20,40-tetrahydroxychalcone, morachalcone A, kuwanon C, cyclomulberrin, dihydrokaempferol, 2,4-dihydroxybenzoic acid, *p*-coumaric acid, moracin J, moracin B and moracin D were found from *Morus alba* twigs. Steppogenin 2, 4, 20, 40-tetrahydroxychalcone, morachalcone A, oxyresveratrol and moracin M have more tyrosinase inhibitor activity than kojic acid. Five compounds present in *Morus alba* have high tyrosinase inhibitory activity (Zhang et al., 2016). Natural α glucosidase inhibitors are less

toxic than the synthetic inhibitors. Deoxynojirimycin (moranoline) a N-containing sugar has intestinal α -glucosidase inhibitory activity. Buds and roots are likely potential sites of deoxynojirimycin biosynthesis. Twig and trunk bark have fairly high α glucosidase inhibitory activities and high levels of active phytoconstituents, excluding deoxynojirimycin. Twig bark can be used to prepare extracts with various medicinal properties (Liu et al., 2015).

Leaves

Imperfect collagen metabolism in diabetics is responsible for delayed wound healing. Injured endothelial, occlusion of capillary vessels, hyperglycemia-induced leukocyte dysfunction, phagocytosis and reduced chemotaxis are responsible for impaired wound healing. Wound healing in diabetes is hampered due to thickening of the basement membrane of the capillaries and arterioles, formation of advanced glycation end-products and inflammatory molecules (TNF α , IL-1) diminishing collagen synthesis. Hyperglycemia changes cellular morphology, granulation tissue is deficient in collagen and reduced production and irregular differentiation of keratinocytes is seen. Leaves of *Morus alba* are effective in diabetes, oxidation, cancer, bacterial infections, helmenthiasis and ulcer. Leaves contain fixed oil, carbohydrate, protein, tannin, alkaloids, flavonoids i.e. apigenin, quercetin, rutin (Figure 1), glycosides and saponins. Apigenin (Figure 1) a flavone found in many plants and vegetables has numerous biomedical uses mainly in proliferation, viral and bacterial infections, wound healing and inflammation. Apigenin increases levels of antioxidants like catalase, superoxide dismutase, glutathione and also reduces cell damage in pancreatic beta-cells. Besides this it increases GLUT4 translocation and preserves beta-cell efficacy (Shukla et al., 2016).

Three flavonol glycosides, quercetin 3-(6-malonylglucoside) rutin and isoquercitrin are antioxidants in the ethanol leaf extract of *Morus alba*. Four new 2-arylbenzofuran derivatives (moracins V–Y) and (moracins N and P) have also been identified. Butanol leaf extract has two new prenyl flavanes and a glycoside with six known compounds i. e. isoquercitrin, astragalol, scopolin, skimmin, roseoside II and benzyl D-glucopyranoside. Methanol leaf extract has ten recognized flavonoids and ethanol leaf extract of *Morus alba* has morachalcones B and C (Chan et al., 2016). Leaves also have considerable amount of proteins (15.31– 30.91%), amino acids like valine, glutamine, leucine, glycine, lysine, lipids (2.09–7.92%) carbohydrates (9.70–39.70%) and neutral

dietary fiber (9.9–36.66%). Leaves are also adequate source of micro and macro nutrients like vitamin C, D and B₁, beta-carotene, calcium, magnesium, potassium, phosphorus, iron and zinc. Leaves have bioactive polyphenols like quercetin, rutin, isoquercetin and astragalins. Rutin has antihyperglycemic activity by increasing insulin, glycogen and hexokinase levels. Isoquercetin controls blood glucose levels, enhances functioning of pancreatic islets and protects against lipid peroxidation and oxidative stress. Three phytoalexins moracins (moracin C, moracin N, chalmoracin) are free-radical scavengers in stressed plants and iminosugars, glycoproteins, ecdysteroids, megastigmanes and volatile compounds also play a role in antidiabetic activity of *Morus alba* plant. *Morus alba* leaves have 1-deoxynojirimycin (Figure 1) which controls postprandial blood glucose levels in diabetic patients. It is an alpha-glycosidase inhibitor and degrades starch and oligosaccharides to monosaccharides before absorption (Liu et al., 2015). Only 6.5 mg of deoxynojirimycin suppresses the elevation of postprandial blood glucose substantially (Vichasilp et al., 2012). *Morus* leaves have 15 bioactive molecules showing effect on alpha-glucosidase (flavones, prenylated stilbenes, and iminosugars). Leaves also contain lupeol, loliolide, beta-sitosterol (Figure 1) scopolin, skimmion, roseoside II, alkaloids (D-fagomine and 3-epi-fagomine, benzyl D-glucopyranoside), coumarins, volatile oil and organic acids (citric, malic, tartaric, oxalic) which are multi target bioactive phytoconstituents. The *Morus alba* extract increases beta cells and sensitizes insulin receptor to insulin (J Mohammadi and PR Naik, 2012). Damage of islets of Langerhans with aqueous extract of plant extract was less congestive (Saenthaweesuk et al., 2009) and plant extract also increases hexokinase activity, glycogen synthesis, reduces lactate and glucose-6-phosphate dehydrogenase (G-6-PD) levels in liver (Hamdy, 2012). Aqueous leaves extract has comparable antidiabetic activity to metformin and glibenclamide (Kumar, 2012). Crude methanol fractions of *Morus alba* exhibits time and dose dependent antidiabetic activity (Shah et al., 2013) and Ethanol extract reduced percentage of blood glucose in comparison to 0.5 mg metformin more than 11.4, 18.8 and 19.3% respectively (Laddha et al., 2012). Ingestion of 1 g plant extract with sucrose 75 g in 500 ml hot water significantly decreases the blood glucose levels over first 120 min (Mudra, 2007).

Morus alba aqueous extract in a dose of 150 mg/kg decreased levels of Triglycerides, Total Cholesterol, Low Density Lipids and High Density Lipoproteins by 35.5, 9.56, 7.30 and 13.16%, respectively, compared with the hyperlipidemic controls (Zeni and Dall'Molin, 2010). Also brew increases the suppression of cell adhesion molecules, vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 expression in the aorta (Lee et al., 2011) and leaf tablets in a dose of 2.3 g per day can be effective alternative therapy in mild dyslipidemia (Aramwit et

al., 2011). Leaves reduced serum Triglycerides by 19.23% compared to baseline data (Kojima et al., 2010) and extract containing quercetin (11.70%), naringenin (9.01%) and gallicocatechin gallate (10.02%) has antiatherogenic activity, inhibits oxidation and lipid peroxidation of LDL, reduces foam cell formation, reduce concentration of triacylglycerol, cholesterol and stimulates expression of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase exhibiting significant antioxidant activity (Yang, 2011).

Prenylated flavonoids 30,8-diprenyl-40,5,7-trihydroxyflavone, kuwanon S (Figure 1) 8-geranyl-pigenin, cyclomulberrin, sanggenon J and K, cyclomorusin, morusin, atalantoflavone and kaempferol present in methanolic extract of *Morus alba* leaves has cytotoxic activity against cancer cells (Dat, 2010). Aqueous, 50% water-methanolic and 100% methanolic extracts satisfactorily inhibits hepatocellular carcinoma and cell proliferation with most potent inhibiting effect on the growth of hepatocellular carcinoma cells shown by 50% water-methanolic and 100% methanolic extracts (Fathy, 2013). Organic extracts reduces growth of hepatoma cells by synchronized actions of inducing cell cycle arrest in the G2/M phase, inhibiting topoisomerase IIa capacity, and inducing caspase cascade and apoptosis mechanisms (Naowaratwattana, 2010).

Ethyl acetate soluble fraction of methanol extract of *Morus alba* leaves reduces intensification and distribution of myonecrosis and myocarditis and increases levels of superoxide dismutase activity from 65 to 161%, also reducing levels of lipid peroxidation from 24.31 to 48% and having protective effect on hypertrophy and degenerative changes on myocardial muscles (Nade, 2013). The plant also decreases concentrations of cardiac markers such as creatine kinase, lactate dehydrogenase reduces lipid peroxidation and restores the decreased level of primary enzymes and molecules involved in reactive oxygen species elimination (superoxide dismutase, glutathione peroxidase, glutathione, catalase) near to normal (Madhumitha and Indhuleka, 2012).

The methanolic leaf extract shows dose-dependent potentiation of haloperidol and metoclopramide induced catalepsy in mice, reduced number of fights and increased latency to fights in foot shock-induced aggression and also prevented contractions induced by dopamine on isolated rat vascular deferens (Yadav and Nade, 2008). Aqueous extract has antimicrobial and antifungal activity (Omidiran et al., 2012) with *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* being

most susceptible bacterial species to crude extract of *Morus alba* with minimum inhibitory concentration ranging from 0.2–26 mg/mL (Jha and Skrivastava, 2013). The ethanolic extract and 1-deoxynojirmycin showed strong bacteriostatic activity against *S. mutans* but 1-deoxynojirmycin had minimum inhibitory concentration value (15.6 mg/mL) 8 times lower than the crude ethanolic extract (125 mg/mL) (Manjula and Shubha, 2011; Islam et al., 2008).

The alcoholic extract from *Morus alba* leaves increases glutathione content by 133.3%, total antioxidant concentrations by 94.8% and decreases the level of thiobarbituric acid by 16.6% (Sadighara et al., 2013). *Morus alba* and curcumin suppress the reactive oxygen species amount increased by resistin in Human Endothelial Cells and reduce two protein (resistin-induced fractaline and P-selectin) expression, important molecules in the inflammatory process in atherosclerosis and diabetes. *Morus alba* extract also decreases the action of NADPH oxidase close to the control level (Gryn-Rynkoa et al., 2016). Thus the extracts can be potential, accessible and safe alternative to synthetic antioxidants and polyunsaturated fatty acids in *Morus alba* leaves may be explored as new dietary supplements and food products (Radojkovi et al., 2016).

Twenty compounds isolated and structure by spectroscopic analysis and the comparison of literature values indicated kaempferol, quercetin, isorhamnetin, norartocarpetin, kuwanon C, astragaln, quercetin-3-*O*-glucopyranoside, kaempferide 3-

O-glucoside, 7, 2', 4'- trihydroxyflavanone, steppogenin, and eight benzofurans, moracin M, wittifuran E, 2-(3, 5-dihydroxyphenyl)-5, 6-dihydroxybenzofuran, moracin N, moracin C, albafuran A, moracin X, morunigrol C, one stilbene, oxyresveratrol and one chalcone, morachalcone A (Figure 1). Morachalcone A has strong pancreatic lipase inhibitory effect. Phenolic compounds in *Morus alba* leaves are flavonoid, benzofuran, stilbene and chalcones. Flavone aglycones has moderate pancreatic lipase inhibition whereas prenylated flavonoid has most potent lipase inhibition. Phenolic compounds are mainly responsible for pancreatic lipase inhibitory action of *Morus alba* leaves (Shukla et al., 2016). Utility of *Morus* leaves can be enhanced by optimal extraction parameters and they could be potential natural antioxidants in medicinal and food industries (Yuan et al., 2015).

Roots

Root bark of *Morus alba* has polyhydroxylated alkaloids, 1-deoxynojirmycin (Asano et al., 1994) and its derivatives, terpenoids, flavonoids, stilbenoids and coumarins (Mohammadi and Naik, 2012). Root bark is effective in diabetes, inflammation, microbial infections and hyperlipidemia. It is also effective in anxiety and depression. *Morus alba* decreases obesity and depression symptoms by regulating metabolic disorders and exhibiting direct effect on the pathogenesis of depression

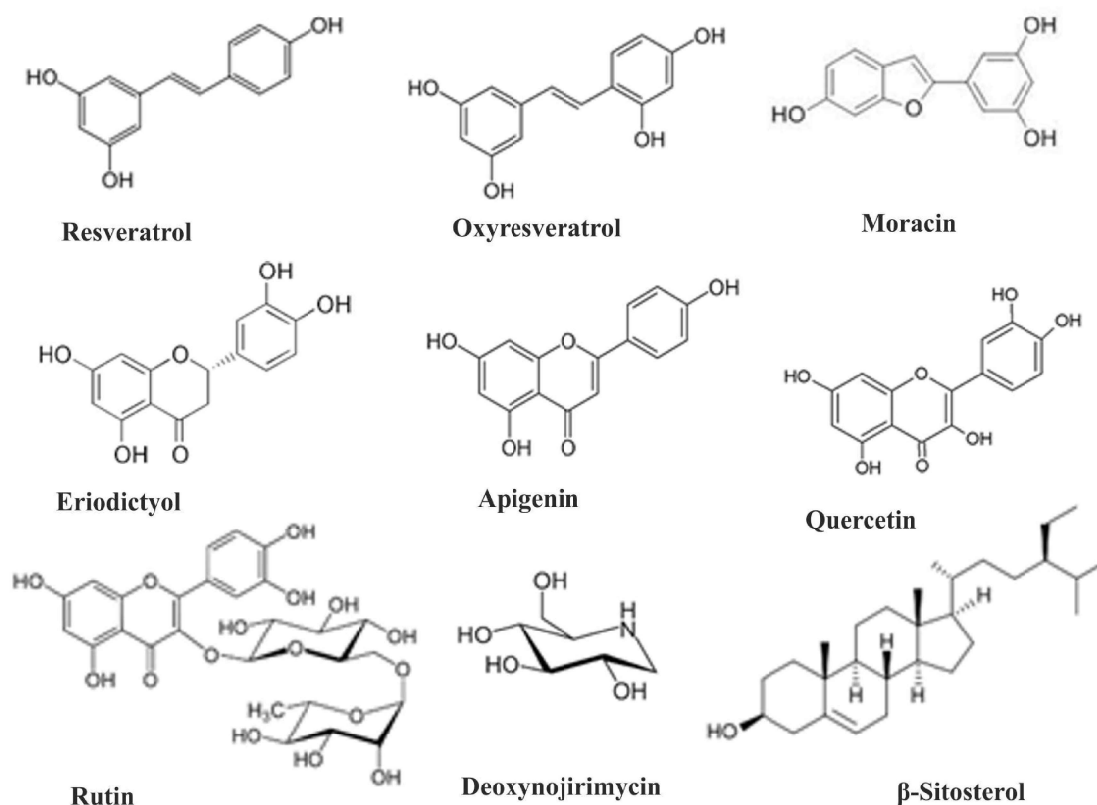


Figure 1. Structures of Phytoconstituents present in *Morus alba*

during diabetes by restoring Brain Derived Neurotrophic Factor levels in the Prefrontal cortex through Extracellular Regulated Kinase and Protein Kinase B signaling pathways (Yea et al., 2016).

Fruits

Fresh fruits extract of *Morus alba* has shown five anthocyanins (Du et al., 2008). Whereas ethanol fruit extract has yielded 25 phenolic compounds, identified from the mulberry fruit for the very first time (Wang et al., 2013).

Pharmacological activities shown by *Morus alba*

Antioxidant properties

Ethanol mature fruit extract is rich in anthocyanins, which are excellent antioxidant agents exhibiting increased free radical scavenging activity than vitamin C (Yea et al., 2016). Based on total phenolic content, free radical scavenging, ferric reducing power and ferrous ion chelating activity, aqueous methanol leaf extracts of *Morus alba* shows significantly higher values than that of fruits (Lye, 2012). The ranking is of the order: developing leaves > young leaves > mature leaves > mature fruits.

Antimicrobial activity

Kuwanon G present in methanol root bark extract has antibacterial activity against oral pathogens such as *Streptococcus mutans*, *Streptococcus sanguis*, *Streptococcus sobrinus* and *Porphyromonas gingivalis* (Park et al., 2003). From the root bark, mulberrofuran G and albanol B strongly inhibit *Salmonella typhimurium*, *Staphylococcus epidermis* and *Staphylococcus aureus* (Sohn et al., 2004). Leaf extracts of *Morus alba* also exhibit antifungal activity (Rao et al., 2012). From eight flavonoids isolated from the root bark of *Morus alba* leachianone G exhibits potent antiviral activity and mulberroside C has weak activity against herpes simplex type 1 virus (HSV-1) (Du et al., 2003).

Skin-whitening properties

Mulberroside F present in methanol leaf extract of *Morus alba* exhibits anti-tyrosinase activity much stronger than kojic acid and also inhibits melanin formation in melana cells (Lee et al., 2002). Oxyresveratrol exhibits an inhibitory activity that is 32-fold stronger than kojic acid (Shin et al., 1998). Oxyresveratrol having four hydroxy groups and resveratrol having three hydroxy groups are two hydroxystilbenes found in *Morus alba*. Also present are norartocarpetin, euchrenone and quercetin showing antityrosinase activity, which is significantly stronger than kojic acid. Morin, resveratrol, maclurin, rutin, isoquercitrin and morin have been isolated from ethanol mulberry twig extract. Resveratrol has skin whitening activity and is also effective in various neurodegenerative and cardiovascular diseases, diabetes and cancer (Wu et al., 2013).

Cytotoxic activity

Quercetin-3-*O*- β -D-glucopyranoside and quercetin-3-7-di-*O*- β -D-glucopyranoside impedes the progress of human leukemia (Kim et al., 2002). A flavanone (7, 2', 4', 6'-tetrahydroxy-6-geranylflavanone) shows cytotoxic activity in rat hepatoma (Kofujita et al., 2004). A novel flavanone glycoside from root bark of *Morus alba* shows anti-proliferative activity (Zhang et al., 2009). Albanol A in root bark of *Morus alba* exhibits cytotoxic and apoptotic activity in human leukemia HL-60 cells. Albanol A also induces early apoptosis with marked reduction in procaspases-3, -8, and -9, and activation of caspase-2. Morusin in root bark initiates apoptosis and suppresses nuclear factor kappa-light-chain-enhancer of activated B cells in human colorectal cancer. Eleven flavonoids from methanol leaf extract of *Morus alba* exhibits cytotoxic activity in human cancer HeLa, MCF-7 and Hep-3B cells. The strongest activities are observed with morusin against HeLa cells, 8-geranylapigenin against MCF-7 cells and sanggenon K against Hep-3B cells respectively. Two new chalcones (morachalcones B and C) present in leaves of *Morus alba* has moderate cytotoxic activity in human cancer HCT-8 and BGC-823 cells. *Morus alba* extracts inhibits nuclear factor kappa B gene expression and significantly decreases α -fetoprotein, γ -glutamyl transpeptidase and alkaline phosphatase in the cells. Methanolic root bark extract of *Morus alba* also shows anticancer activity by inducing cell growth arrest and apoptosis in human colorectal cancer SW480 cell (Chan et al., 2016).

Neurodegenerative disorders

Oxyresveratrol demonstrated neuroprotective activity in cortical neuronal cells in the in vivo and in vitro models and also in SHSY5Y cells (Zou et al., 2012). It was observed that the methanol extract of *Morus alba* leaves exerts antidopaminergic effect by blocking D2 receptors. Oxyresveratrol has a neuroprotective effect against Alzheimer's disease and stroke. Ethanol fruit extract treated rats show improvement in memory test performance in the water maze test and decreased activity of acetylcholinesterase and also increase density of neurons in the hippocampus (Kaewkaen et al., 2012; Kaewkaen et al., 2012b; Wattanathorn et al., 2012). Extracts of the mulberry leaf are also used to relieve headaches, depression, schizophrenia and its action is comparable with the effect of clozapine (Laddha and Vidyasagar, 2012a).

Anti-inflammatory activity

Methanolic root bark extract exhibits anti-inflammatory activity mediated via inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells and initiation of ERK1/2.

Kuwanons C and G possess anti-inflammatory activity. Mulberroside A and oxyresveratrol show anti-inflammatory effect on carrageenin-induced paw edema in rats may be due to inhibition of the nitric oxide synthase expression through down-regulation of NF- μ B binding activity and significant inhibition of Prostaglandin E2 synthesis (Chung et al., 2003). Methanolic branch extract of *Morus alba* with active compound oxyresveratrol have anti-inflammatory activity (Chen et al., 2013) which might be because of inhibition of CXCR- 4-mediated chemotaxis and mitogen-activated protein kinases/extracellular signal-regulated kinases pathway in T and other immune cells (Chan et al., 2016).

Anti-diabetic activity

Leaf extract has substantial postprandial hypoglycemic effect possibly through the inhibition of α -glucosidase and glucose transport (Park et al., 2009). *Morus alba* leaf extract restores the diminished number of β -cells (Mohammadi and Naik, 2008). Aqueous ethanol leaf extract of *Morus alba* reduces blood glucose levels of type II diabetic rats and the effect may be due to chlorogenic acid and rutin present in the extract (Hunyadi et al., 2012). Zucker diabetic fatty rats treated with mulberry fruit extract for five weeks showed significantly lower glucose levels than control group (Sarikaphuti et al., 2013). Ethanol fruit extract significantly decrease blood glucose and serum protein and increases antioxidant enzymatic levels in streptozotocin induced diabetic mice. Anti-diabetic activity of the fruit extract might be due to potent α -glucosidase inhibition (Wang et al., 2013). In one study blood glucose concentration of the healthy humans and the type-2 diabetic patients after taking 75 g sucrose in 500 mL of hot water using 1 g of *Morus alba* leaf extract or placebo were monitored. Significant difference in the blood glucose levels between *Morus alba* and placebo over the first 120 min was observed (Mohammadi and Naik, 2012). In another clinical study hypoglycemic effects of *Morus alba* leaf extract on postprandial glucose and insulin levels in patients with type 2 diabetes treated with sulfonylurea hypoglycemic agents was conducted. Results showed postprandial glucose and insulin levels in type 2 diabetic patients treated with sulfonylurea were markedly reduced after the ingestion of jelly containing 3.3 g of leaf extract compared to ingestion of placebo jelly by diabetic patients and healthy subjects (Nakamura et al., 2011). 1-Deoxyojirimycin present in *Morus alba* leaves, is a potent glucosidase inhibitor and suppresses unusually high blood glucose levels thereby averting diabetes mellitus. Only single administration of 0.8 and 1.2 g of Deoxyojirimycin enriched powder significantly prevented increase of postprandial blood glucose and secretion of insulin. Thus Deoxyojirimycin enriched powder can be used as a dietary supplement in antidiabetic therapy (Kimura et al., 2007). 1-Deoxyojirimycin

from leaves regulates hepatic gluconeogenesis enzymes, glucokinase, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. *Morus alba* also stimulates differentiation of 3T3-L1 preadipocytes into adipocytes, enhances insulin sensitivity by secretion of adiponectin from 3T3-L1 adipocytes and reduces insulin resistance (Naowaboot et al., 2012).

Anti-hyperlipidemic activity

Mulberroside A from ethanol root extract of *Morus alba* and its aglycone derivative (oxyresveratrol) from mulberroside A by enzymatic conversion have been tested for their anti-hyperlipidemic effects. Oral pre-treatment with mulberroside A or oxyresveratrol (1–5 mg/kg) significantly reduces serum lipids levels in hyperlipidemic rats and in high-cholesterol diet treated hyperlipidemic rats. Oxyresveratrol also show serum lipid lowering capacity than mulberroside A supporting the hypolipidemic effects of the root bark and hypotriglyceridemic effects of leaves (Jo et al., 2014; El-Beshbishy et al., 2006; Zeni and Dall'Molin, 2010).

Anti-atherosclerotic activity

Beneficial effect of dietary intake for twelve weeks of 1% *Morus alba* leaf powder on atherogenesis in apolipoprotein E-deficient mice have been reported, appreciably increasing lag time of lipoprotein oxidation in the *Morus alba* extract treated group compared with control group. Extract treated group also shows forty percent reduction in atherosclerotic lesion size in the aorta. Thus antioxidative compounds in *Morus alba* with strong free radical scavenging and lipoprotein oxidation inhibition activity can help prevent atherosclerosis (Harauma et al., 2007). Water extract lower the serum cholesterol and triglyceride and suppress progression of atherosclerosis in high cholesterol diet-fed rabbits, maybe due to preventative effect of anthocyanins against Low Density Lipoprotein-oxidation in the arterial wall. Hence water extract might be explored for lowering the incidence of atherosclerosis and coronary heart disease. In one study the levels of triglyceride, cholesterol and low-density lipoprotein in the serum of rabbits treated with fruit extract were lower than that in the control group. Similarly freeze-dried mulberry fruit powder (5% and 10%) lowered serum and liver total cholesterol, triglyceride, inhibited lipid peroxidation and increased antioxidant enzyme activity in rats, repressing development of atherosclerosis in hyperlipidemic rats (Chen et al., 2005).

Anti-obesity activity

Ethanol leaf extract effect has been studied for melanin-concentrating hormone receptor activity and obesity in diet-

induced obese mice. Hormone receptor assay show that the extract (10–100 $\mu\text{g}\cdot\text{mL}^{-1}$) has potent inhibitory activity, with IC50 value being 2.3 $\mu\text{g}\cdot\text{mL}^{-1}$. In other anti-obesity study, administration of the extract for 32 consecutive days caused decrease in body weight and adiposity and regulated hepatic lipid buildup in the mice. The effect of extract in obesity might be due to receptor antagonism (Oh et al., 2009). *Morus alba* water extract possesses the potential of improving obesity-related metabolic syndromes (Peng et al., 2011). Combined leaf and fruit extract of *Morus alba* demonstrated positive beneficial effects on obese mice. The extract ameliorated cholesterol transfer proteins and reduced oxidative stress in the obese mice fed daily with the extract at 500 mg per kg for 12 weeks (Valacchi et al., 2014).

Hepatoprotective activity

Alcoholic and water extracts of *Morus alba* possess hepatoprotective activity. The extracts prevented the biochemical and histological changes induced by Carbon tetrachloride in the liver (Hogade et al., 2010). The protective

mechanisms of aqueous *Morus alba* fruit extract on oral administration (0.5%, 1%, and 2%) is by significantly reducing lipid peroxidation, inhibiting lipid deposition and liver fibrosis. The extract also diminishes the expression of pro-inflammatory genes such as COX 2, nuclear factor kappa B, and inducible Nitric oxide synthase. Hepatoprotective effect of leaves of *Morus alba* have been reported earlier also (Hsu et al., 2012).

Other pharmacological activities

Other pharmacological properties of *Morus alba* include antiplatelet, anxiolytic, anti-asthmatic, anthelmintic, antidepressant, immunomodulatory and cardioprotective activities (Chan et al., 2016).

Conclusion

Recently there is an increasing interest in natural drugs due to their potential efficacy and fewer side effects. Pharmaceutical industry is focusing on isolation of bioactive phytoconstituents for commercial use in various ailments. *Morus alba* is a multi-utility plant and its various parts are

Table 1. Pharmacological activities of *Morus alba*

Activities	Plant part used	Activity Model	References
Anti-inflammatory activity	Twig, Root	Carageenan in mice	Chen et al., 2013; Chung et al., 2003
Antioxidant activity	Twig, Leaves, Fruit	Ferrous ion chelating activity, ferric reducing power	Chang et al., 2001; Yang, 2011; Yea et al., 2016; Lye, 2012
Anti-cancer activity	Leaves, Root	Hepatocellular carcinoma cells, hepatoma cells leukemia HL-60 cells	Dat, 2010; Naowaratwattana, 2010; Chan et al., 2016
Antihyperlipidemic activity	Leaves, Root	High-cholesterol diet treated hyperlipidemic rats	Zeni and Dall'Molin, 2010; Jo et al., 2014
Antimicrobial activity	Leaves, Root	<i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Streptococcus mutans</i> , <i>Streptococcus sanguis</i> , <i>Streptococcus sobrinus</i>	Omidiran et al., 2012; Park et al., 2003
Neuroprotective activity	Leaves	Foot shock-induced aggression Water maze test	Yadav and Nade, 2008; Kaewkaen et al., 2012
Anti-diabetic activity	Twig, Leaves, Root, Fruit	Alloxan induced diabetes, Brain Derived Neurotropic Factor, Zucker diabetic fatty rats	Liu et al., 2015; Shukla et al., 2016; Vichasilp et al., 2012; Mohammadi and Naik, 2012; Kumar, 2012; Yea et al., 2016; Sarikaphuti et al., 2013
Anti-atherosclerotic activity	Leaves, Fruit	Human Endothelial Cells	Rynkoa et al., 2016; Harauma et al., 2007; Chen et al., 2005
Anti-obesity activity	Leaves, Fruit	Diet-induced obese mice Obese mice	Oh et al., 2009; Valacchi et al., 2014
Tyrosinase inhibitory activity/ Skin whitening activity	Twig, Leaves	Melanin formation in melana cells	Zhang et al., 2016; Lee et al., 2002
Hepatoprotective activity	Fruit, Leaves	Carbon tetrachloride in Rats	Hogade et al., 2010; Hsu et al., 2012
Cardioprotective activity	Leaves	Cardiac markers	Madhumitha and Indhuleka, 2012

effective in oxidation, microbial infection, as skin-whitening agent, cytotoxicity, inflammation, diabetes, hyperlipidemia, atherosclerosis, obesity, hepatotoxicity and cardiovascular diseases. It can be considered as an alternative natural drug for various purposes. Though clinical trials on humans have been conducted further research will establish more benefits of this plant and will throw light on chemical constituents responsible for each medicinal activity. Multi drug approach is needed in many ailments. *Morus alba* can be explored for synergistic activity with conventional drugs and also whether combination reduces adverse effects of existing drugs. Also authentication and standardization of extracts poses a problem, still each part of this plant has significant pharmacological and medicinal activity and thus it can be called as a miracle drug. *Morus alba* twig and its phytoconstituents may be explored as potential sources in nutraceuticals and cosmeceuticals particularly as inhibitors of tyrosinase activity in food products and in cosmetics as skin-whitening agents (Zhang et al., 2016). However limited preliminary clinical experiments on humans and animals have been conducted. Many bioactive compounds present in the *Morus alba* leaves may be potential candidates for range of novel and innovative drug development. They can also be used as starting materials for the production of easily bioavailable, safe and dedicated nutraceuticals. In spite of so much accumulated knowledge there is still scope for researching undiscovered conformationally unstable structures, chiral molecules and understanding mechanisms responsible for their biological activity (Gryn-Rynkoa et al., 2016). Further research can focus on preparing high quality *Morus alba* twigs for increasing functionality, stability, and bioavailability by microbial fermentation (Choi et al., 2013).

Future direction

This review contains detail about phytoconstituents present in various parts of plant and detailed pharmacological activity of *Morus alba* has been stated. Though plant is effective in various ailments there is still scope to explore the unexplored potential of the plant due to numerous phytoconstituents present. The effect of all the phytoconstituents has not been explored yet. The knowledge of *Morus alba* plant should be documented properly for future references. As newer molecules get isolated pharmacological activity can be attributed to specific phytoconstituents and new pharmacological activities may be researched accordingly. Also plant as a whole may also be researched further contributing in healthcare of humans in an economic and safe way.

Conflict of interest

The authors declare that they don't have any conflict of interest.

Author contributions

This manuscript has been exclusively prepared by both the authors only.

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