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Review

Traditional uses, phytochemistry and pharmacology of *Morus alba* Linn.: A review

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The leaves of *Morus alba* Linn. (Family: Moraceae) commonly known as mulberry, are mainly used as food for the silkworms and they are sometimes eaten as vegetable or used as cattle fodder in different parts of the world. *M. alba* Linn. has potential source of food diet and natural antioxidants. Many research works have been done on plants, which provide humans with extensive and fundamental uses. The authentic product or by-product of plants serves human beings in so many ways, one of which is medicine. The use of plants for health purpose started long time ago, probably at the first moment when a human being got sick. Some 3,000 years before the present time (B.P), humankind was well aware of the medicinal properties of some plants growing around him. The use of plants to cure diseases and relieve physical sufferings has started from the earliest times of mankind's history. The present article, including the detailed exploration of Phyto-pharmacological properties of *M. alba* L. is an attempt to provide a direction for further research.

Key words: *Morus alba,* mulberry, natural antioxidants, Phyto-pharmacological properties

INTRODUCTION

Over the years, medicinal plants have been found useful in the treatment and management of various health problems. About 80% of the world population relies on the use of traditional medicine, which is predominantly based on plant material (WHO, 1993). Scientific studies available on a good number of medicinal plants indicate that promising Phytochemicals can be developed for many health problems (Gupta et al., 1994). Plants produce a diverse range of bioactive molecules, making them a rich source of different types of medicines. A rich heritage of knowledge to preventive and curative medicines was available in ancient scholastic works included in the Atharva veda, Charaka, Sushruta etc. Over 50% of all modern clinical drugs are of natural product origin (Stuffness and Douros, 1982) and natural products play an important role in drug development programs in the pharmaceutical industry (Baker et al., 1995). Herbal drugs have gained importance in recent years because of their efficacy and cost effectiveness.

The present attempt is to review and compile updated information on various aspects of *Morus alba* L., a plant used all over the world. This plant is commonly known as Mulberry or White-Mulberry, and is generally used as a food source for silkworms and abundantly available throughout most parts of Asia.

Morus alba L.

The genus *Morus* contains approximately 16 members of family Moraceae, occurring primarily in northern temperate regions with some extending into tropical areas of Africa and the South American Andes. There are 11 species distributed widely in China. Genus *Morus* (Mulberry) is one of such example that consists of over 150 species, among these, *M. alba* L. is dominant (Srivastava et al., 2006). Generally, it is used as foliage to feed the silkworms (*Bombyx mori* L.) and ruminants (Arabshahi-Delouee and Urooj et al., 2007). In many

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countries like Turkey and Greece, *M. alba* and other Mulberries are grown for fruit production that have certain application in some traditional foodstuffs (Anonymous, 2001).

Synonyms

Morus macrophylla Moretti, *M. morettiana Jacq*. and *M. nervosa Deles*.

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Urticales
Family: Moraceae
Genus: *Morus*
Species: *Morus alba*

Vernacular names

Sanskrit: Toola, Tula; Hindi: Chinni, Tut, Tutri; Bengali: Tut; Marathi: Tut, Ambat; Gujarati: Shetur; Telegu: Reshme chettu, Pippalipandu chettu; Tamil: Kambli chedi; Kannada: Bili uppu nerale; Punjabi: Tut, Tutri; Oriya: Tuto, Tuticoli; English: Mulberry, White mulberry.

Distribution

It is a native to Pakistan, India and Nepal, east-wards to Mayanmar (Barma), Indochina, China and Japan. It is extensively cultivated throughout the plains of India and Pakistan, and in the Himalayan hills up to 3,300 m elevation for its foliage, which is used as a food source for silkworm s, also cultivated in Europe and throughout most of Asia, and is occasionally naturalized (Anonymous, 2001).

Cultivation

Mulberry trees can be propagated by seeds, cuttings, or graftings. Seeds should be treated with camphor water before sowing to ward off disease. Thin layer of soil and ashes spread over seed after sowing. Beds are kept moist. Seeds germinate in 9 to 14 days, depending on the season. When seedlings are about 7.5 cm tall, they are thinned and weeded. For bush mulberries, seedlings 10 to 15 cm tall are used as transplants; for trees, seedlings are allowed to grow 1.3 m and trained before transplanting. Branches are cut into pieces 22 to 30 cm long with 3 buds and planted immediately. Mulberry plants from seedlings are more expensive, but give better plants than those from cuttings. Root grafting is usually practiced in India. Rooted cuttings are planted in pits or furrows.

When irrigation is used, cuttings are planted in furrows in April or May, 10 cm apart, the furrows being 22 cm apart. With this very close planting, 110,000 to 200,000 cuttings/ha are required. Grafted plants develop a better root system than those from seedlings, cuttings, or layering, and are used exclusively in Japan. Grafted trees are planted 1.6 m apart each way, about 4,000/ha, and are especially suitable for irrigated areas. Various techniques are employed to prune and train mulberry plants. After each pruning, the field is cultivated and manured (Anonymous, 2001).

PLANT DESCRIPTION

The plant is usually a monoecious shrub or a medium sized tree with a cylindrical stem and rough, brown, vertically fissured bark. Leaves are variable in size and shape, usually 5 to 7.5 cm long, often deeply lobed, margins serrate or crenate-serrate, apex acute or shortly acuminate, base cordate or truncate; 3 basal nerves, lateral nerves forked near the margins. Flowers are inconspicuous and greenish: male spikes (catkins) are broad, cylindrical or ovoid, female spikes are ovoid and stalked. Fruit (syncarp) consists of many drupes enclosed in a fleshy perianth, ovoid or subglobose, up to 5 cm long, white to pinkish white, purple or black when ripe (Anonymous, 2001).

Reported phytoconstituents

The leaves are a good source of ascorbic acid, with 2 to 3 mg/g, of which over 90% is present in the reduced form. They contain carotene, vitamin B_1, folic acid, folinic acid, and vitamin D. Volatile constituents identified in steam-distillates of the leaves are n-butanol, beta-gamma-hexenol, methyl-ethyl acetaldehyde, n-butylaldehyde, isobutylaldehyde, valeraldehyde, hexaldehyde, alpha-beta-hexenal, methyl-ethyl ketone, methyl-hexyl ketone, butylamine, and acetic, propionic and isobutyric acids. The leaves also contain calcium malate, succinic, and tartaric acids, xanthophyll and isoquercitrin (quercetin 3-glucoside) and tannins (Anonymous, 2001).

New polyhydroxylated alkaloids, (2R,3R,4R)-2-hydroxymethyl-3,4-dihydroxy-pyrrolidine-N-propionamide from the root bark of *M. alba* L., and 4-O-α-D-galactopyranosyl-calystegine B2 and 3β,6β-dihydroxynortropane from the fruits, were isolated by column chromatography using a variety of ion-exchange resins. Fifteen other polyhydroxylated alkaloids were also isolated (Asano et al., 2001). 1-deoxynojirimycin (DNJ), a polyhydroxylated piperidine alkaloid present in both leaves and bark, is known to be one of the most potent α-glycosidase inhibitors (Oku et al., 2006). A prenylated flavonoid, moralbanone, along with seven known compounds kuwanon S, mulberroside C, cyclomorusin, eudraflavone B hydroperoxide, oxydihydromorusin, leachianone G and alpha-acetyl-amyrin were isolated from the root bark of *M. alba* L. (Du et al., 2003). A new glycoprotein was purified from the aqueous methanolic extract of the root bark of *M. alba* which has been used as a component of antidiabetic remedy in Oriental medicine.

This new glycoprotein was named as Moran 20K (Kim et al., 1999). Mulberrofuran G and albanol B were isolated from the root bark of *M. alba* L. (Moraceae) (Chi et al., 2001). The purity of isolated compounds evaluated by reversed-phase high-performance liquid chromatography (HPLC) was above 95% (w/w) and the structure of prenylated flavonoids used in the study was identified by spectral data analysis (Sohn et al., 2004).

Anthocyanins in the fruits of mulberry (*M. alba* L.) were extracted and separated by high speed counter-current chromatography (HSCCC), using a biphasic solvent system composed of methyl tert-butyl ether-n-butanol-acetonitrile-water trifluoroacetic acid (1:3:1:5:0.001) to yield five anthocyanins which are cyanidin 3-O-(6''-O-α-rhamnopyranosyl-β-D-glucopyranoside), cyanidin 3-O-(6''-O-arhamnopyranosyl- β-D-galactopyranoside), cyanidin 3-O-β-D glucopyranoside, cyanidin 3-O-β-D-galactopyranoside and cyanidin 7-O-β-D-glucopyranoside, respectively.

The five compounds were identified by electrospray ionization mass spectrometry (ESI-MS) and one/two-dimensional Nuclear magnetic resonance (NMR) spectra (Qdu and Zheng, 2008). A novel prenylated flavanone was isolated from ethyl acetate extracts of the hard-wood cutting root of Kinuyutaka, a cultivar of *M. alba*. The structure, 7, 2', 4', 6'-tetrahydoroxy-6-geranylflavanone, was characterized by spectral analyses. This prenylated flavanone exhibited cytotoxic activity against rat hepatoma (dRLh84) cells with an IC_{50} of 52.8 μg/ml (Kofujita et al., 2004). A diglucoside of a 2-arylbenzofuran derivative was isolated from the leaf extract partitioned with dichloromethane, butanol and water in succession.

The active fraction, butanol layer was further separated by silica gel column chromatography and then subjected to column chromatography on Sephadex LH-20 to afford the diglucoside of a 2-arylbenzofuran. The structure of the compound was determined by comparison of its mps, ultra violet (UV), and NMR spectral data with those reported in literature (Lee et al., 2002) (Figure 1).

Medicinal uses

Mulberry leaves are expectorant, encouraging the loosening and coughing up of catarrh, and are prescribed in China as a treatment for coughs. The leaves are also taken to treat fever, sore and inflamed eyes, sore throats, headaches, dizziness and vertigo. The fruit juice is cleansing and tonic, and has often been used as a gargle and mouthwash. The root bark may be used for toothache, and it is considered laxative. An extract of the leaves has been given by injection for elephantiasis. The twigs are efficacious to combat excess fluid retention and joint pain.

The fruit is useful to prevent premature graying of the hair and to treat dizziness, ringing in the ears, blurred vision and insomnia. The root reportedly possesses anthelmintic and astringent properties. The bark is beneficial as a vermifuge and purgative. The leaves are antibacterial, diaphoretic and hypoglycaemic. The stems are antirheumatic, antispasmodic, diuretic, hypotensive and pectoral. The fruit has a tonic effect on kidney energy. It is prescribed in the treatment of urinary incontinence, dizziness, insomnia due to anaemia, neurasthenia, hypertension and diabetes. The root bark is antiasthmatic, antitussive and sedative (Anonymous, 2001).

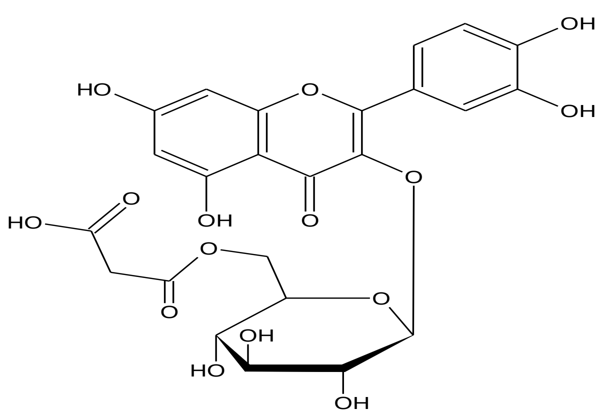
PHARMACOLOGICAL PROPERTIES

Many pharmacological studies have been reported for the different extracts and phytochemical constituents of *M. alba* L. A summary of the reported biological activities is described below.

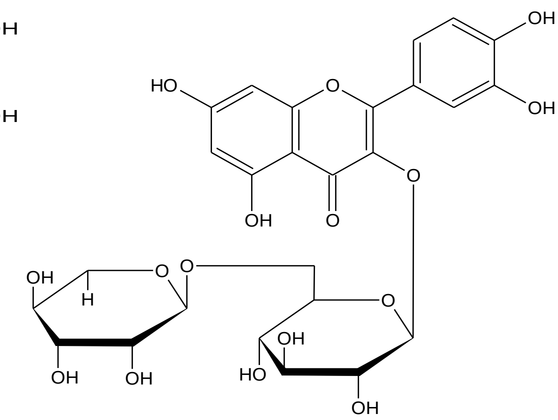
Antidiabetic activity

Mulberry plants play their role by means of various routes such as reduction in food intake and reduce absorption of blood glucose (Lee et al., 2002). Much of action attributed to some functional components like 1-deoxynojirimycin (DNJ), a polyhydroxylated piperidine alkaloid present in both leaves and bark, is known to be one of the most potent a-glycosidase inhibitors (Oku et al., 2006). A human study indicated that the single oral administration of 0.8 and 1.2 g of DNJ-enriched powder significantly suppressed the elevation of postprandial blood glucose and secretion of insulin (Kimura et al., 2007). Root bark of *M. alba* also possess promising hypoglycemic activity. Dose of 600 mg/kg/day of 70% alcohol extract of the *M. alba* root bark to diabetic rats for 10 consecutive days reduced the amount of the glucose by 59% as compared to control, and increased insulin production by 44% (Singab et al., 2005).

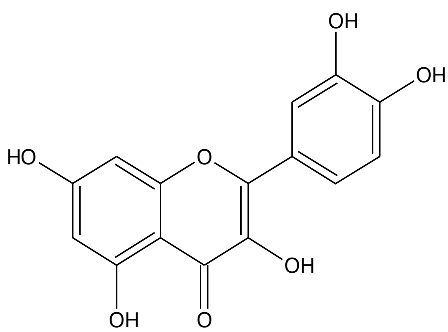
Moran 20K, a protein purified from the aqueous methanolic extract of root bark of *M. alba* has the potential to lower blood glucose level in streptozotocin-induced hyperglycemic mice model. Composition of Moran 20K is also of significant importance as it contains above 20% serine and cysteine similar to that of insulin



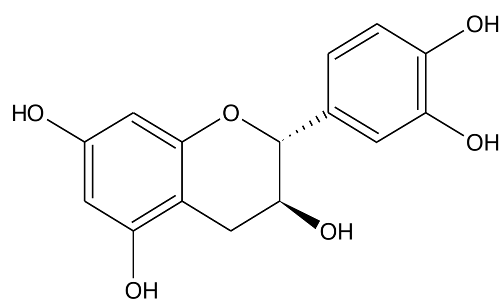
Quercetin 3-(6-malonylglucoside)



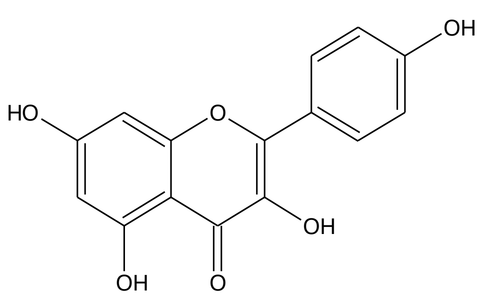
Rutin



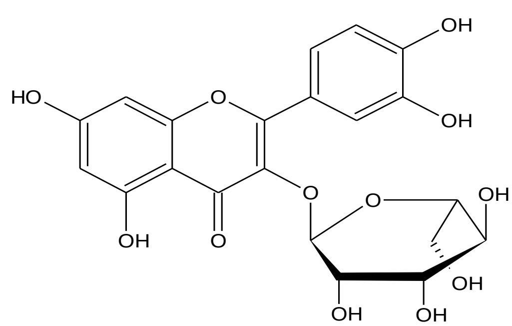
Quercetin



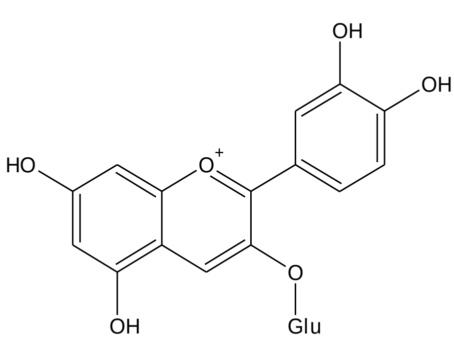
Catechin



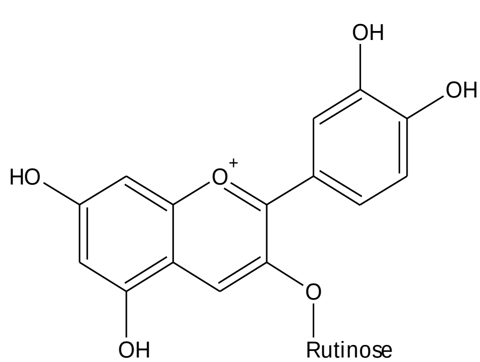
Kaempferol



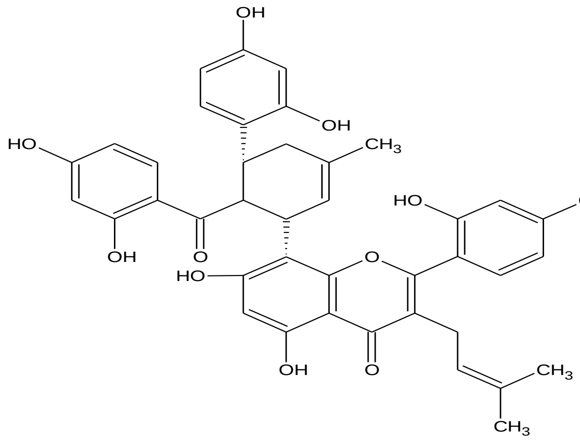
Quercitrin



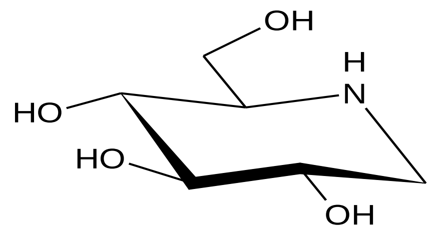
Cyanidin 3-glucoside



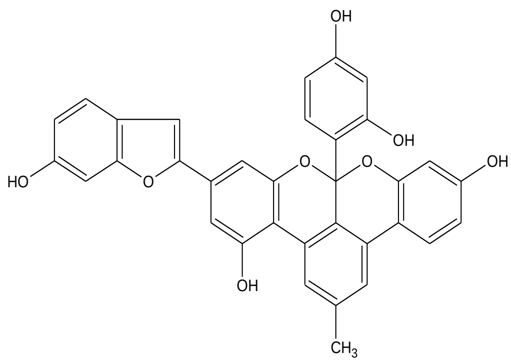
Cyanidin 3-rutinoside



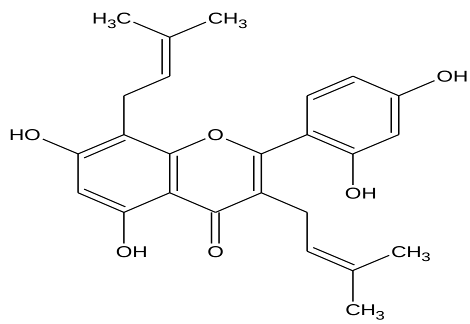
Kuwanon G



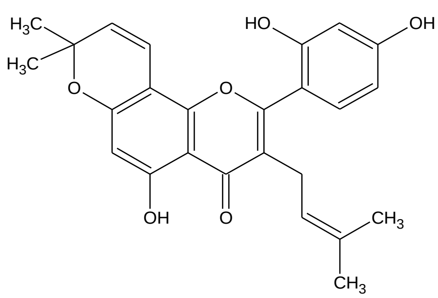
1-deoxynojirimycin



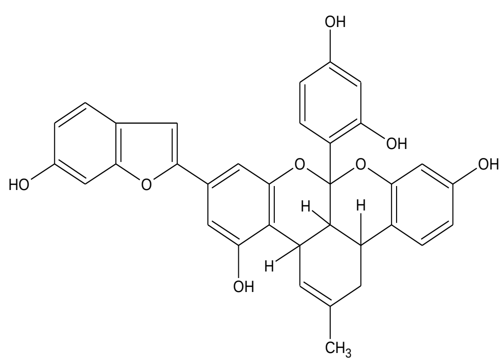
Albanol B



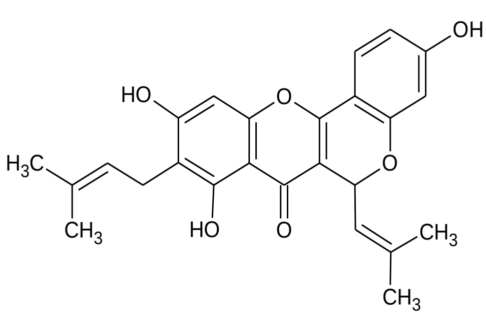
Kuwanon C



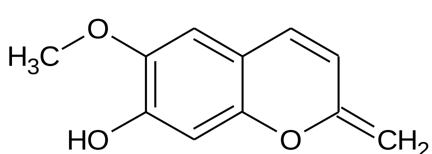
Morusin



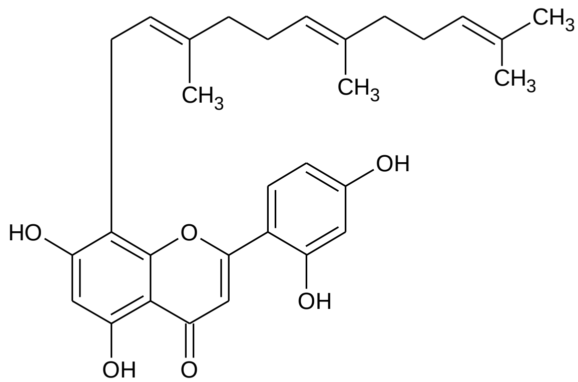
Mulberrofuran G



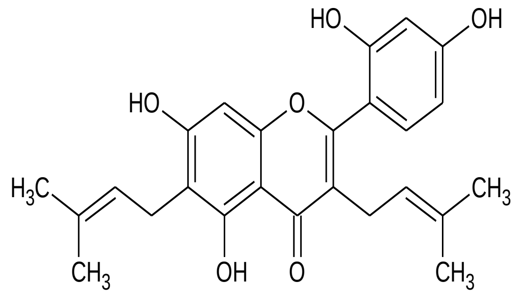
Cyclomulberrin



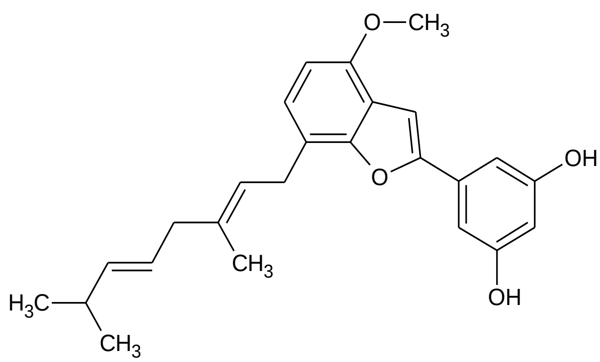
6-methoxy-7-hydroxycaumarin



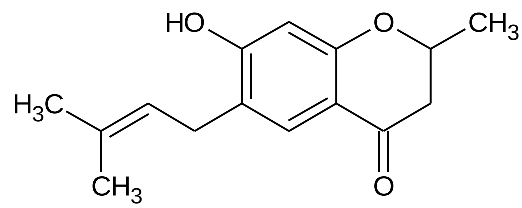
Moralbanone



Mulberrin



Mulberrofuran



7,2’,4’,6’- tetrahydroxy-6-geranylflavanone

Figure 1. Chemical structures of the reported phytoconstituents of *Morus alba* L.

that further ensures its chances of utilization in hyperglycemic patients (Kim et al., 1999).

The possibility of preventing the onset of diabetes and obesity using natural dietary supplements containing 1-deoxynojirimycin and other α-glucosidase inhibitors in high concentration is of great potential interest (Asano et al., 2001). Mulberry leaves and their components hold some interesting mechanism of action regarding their antidiabetic potential. They reduce the blood glucose by increasing the insulin concentrations indicating that they have insulinotropic properties. On the other hand, its antioxidant potential can yield protection against complications of diabetes mellitus.

Antimicrobial activity

Mulberry leaves contained kuwanon C, mulberrofuran G and albanol B, and all showed strong antibacterial activity with minimum inhibitory concentrations (MIC’s) ranging from 5 to 30 mg/ml (Sohn et al., 2004). Various fractions of mulberry such as chloroform extract had strong antimicrobial activities against *Bacilllus subtilis*, and fractions extracted with acetic acid against *Staphylococcus aureus*, *B. subtilis* and *Escherichia coli* (Kim et al., 1993). Morusin, kuwanon C, sanggenon B and D, bioactive molecules from *Morus* bark, possess strong antimicrobial activity against *S. aureus*, *Streptococcus faecalis*, *B. subtilis*, *Mycobacterium smegmatis* and some molds species (Nomura et al., 1988).

Antioxidant activity

Mulberry leaves contained prenylflavanes and prenylflavane glycoside, quercetin 3-O-β-D-glucopyranosyl-(1/6)-β-D-glucopyranoside and quercetin reduce *in vitro* and *in vivo* oxidation process (Doi et al., 2001; Kim et al., 1999). Water extract of *M. alba* leaves had the highest antioxidant properties through ferric reducing/antioxidant power assay (Wattanapitayakul et al., 2005). In some other assays, ethanolic extract contains 5,7-dihydroxycoumarin 7-methyl ether and oxyresveratrol and they scavenge superoxide (Oh et al., 2002). Mulberroside A and oxyresveratrol showed inhibitory effect against $FeSO_4/H_2O_2$-induced lipid peroxidation in rat microsomes and a scavenging effect on DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical (Chung et al., 2003).

Atherosclerosis

M. alba leaves extracts are important in stopping atherosclerosis as they inhibit oxidative modification of low density lipoprotein (LDL). Dietary consumption of *M. alba* leaves and major flavonol glycoside, quercetin 3-(6-malonylglucoside) are associated with reduced atherosclerotic lesion area through enhancement of LDL resistance to oxidative modification in LDL receptor-deficient mice (Katsube et al., 2006; Enkhmaa et al., 2005). Butanolic extract of mulberry leaves scavenged the DPPH radical and inhibited the oxidative modification of rabbit and human LDL (Doi et al., 2000; Katsube et al., 2006). Quercetin and its conjugates are major representatives of the flavonol group of mulberry. These flavonoids exhibited strong inhibitory effects on oxidative modification of human LDL *in vitro* (Naderi et al., 2003; Day and Williamson, 2001; Moon et al., 2001).

Immunonutrition and anticancer activities

Hepatoma is a primary malignancy (cancer) of the liver (Kofujita et al., 2004) isolated 7, 2', 4', 6'-tetrahydoroxy-6-geranylflavanone, a prenylated flavanone, from ethyl acetate extracts of *M. alba* root. This prenylated flavanone exhibited cytotoxic activity against rat hepatoma cells with an IC_{50} of 52.8 mg/ml. Oxyresveratrol from *M. alba* at the concentration of 10 mg/ml reported to inhibit Inducible nitric oxide synthase (iNOS) and COX-2 activity (Chung et al., 2003). Methanolic extract from *M. alba* leaves and its subfractions (chloroform, butanol, and aqueous fractions) inhibited NO production and significantly decreased the production of TNF-a in LPS-activated RAW264.7 macrophages (Choi and Hwang, 2005). Polysaccharide of *M. alba* (PMA) root bark potentially increased lymphocyte proliferation and decreases antibody production from B cells. Both of these activities played an important role in its anti-inflammatory potential (Kim et al., 2000).

Neuroprotective activity

Cyanidin 3-O-β-D-glucopyranoside (C3 G) presented free radical scavenging and inflammation suppressing activity and protected brain from endothelial dysfunction (Seeram et al., 2001; Serraino et al., 2003). Utilization of mulberry leaves reduces the risk of Alzheimer's disease. Mulberry leaf extract provided a viable treatment for Alzheimer's disease through the inhibition of amyloid beta-peptide (1e42) fibril formation and attenuation of amyloid β-peptide (1e42)-induced neurotoxicity (Niidome et al., 2007).

Skin toning activity

Extracts from leaves and root barks of mulberry exhibited high inhibition on the 3,4-dihydroxyphenylalanine (DOPA) oxidase activity and antityrosinase activity (Lee et al., 2002). Oxidative stress caused by free radicals was proposed for hyperpigmentation.

The extract of mulberry (*M. alba* L.) from leaves or root barks (*Mori radicis* cortex) showed free radical scavenging and antioxidant activities thus, beneficial for depigmentation (Andallu and Varadacjaryulu, 2003; Fang et al., 2005). Hyperpigmentation is associated with melanin biosynthesis and Lee et al. (2002) investigated *in vitro* effects of 85% methanol extract of dried *M. alba* leaves on melanin biosynthesis. These extracts inhibited the tyrosinase activity that converts DOPA to dopachrome in the biosynthetic process of melanin. Mulberroside F isolated from mulberry leaves might be used as a skin whitening agent.

Hepatoprotective activity

Extracts from leaves of *M. alba* exhibited hepatoprotective activity. Carbon tetrachloride produced significant changes in biochemical parameters (increases in serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alanine phosphatase (ALP) and serum bilirubin) and histological (damage to hepatocytes), using Standard drug Liv-52. Pretreatment with alcoholic and aqueous extracts significantly prevented the biochemical and histological changes induced by CCl_4 in the liver. The present study shows that the alcoholic and aqueous extracts possessed hepatoprotective activity (Hogade et al., 2010).

Anxiolytic and antidepressant activities

The effects of an aqueous extract of *M. alba* leaves green tea (ME) on mouse behaviors (depression, anxiety, climbing activity and thermal response), muscle coordination and muscle strength were studied (Yadav et al., 2008). Male imprinting control regions (IRC) mice received a single intraperitoneal injection of either the ME, desipramine or diazepam. Thirty minutes after injection, the mice were tested in all experimental models. A significant antidepressant-like effect could be detected in the animals receiving either 100 or 200 mg/kg ME. The effect of 200 mg/kg ME in decreasing the immobility time was comparable to 10 mg/kg desipramine in the elevated plus maze, no increase in time in the open arm could be observed in mice treated with ME at either 100 or 200 mg/kg. However, high doses of ME (500 or 1000 mg/kg) decreased at both times in the open arm and the number of entries in the maze. No change in thermal response was seen in mice treated with ME at doses up to 500 mg/kg, however, at 1000 mg/kg, the response time to heat was increased significantly. The ME at either 500 or 1000 mg/kg also decreased muscle coordination, strength and climbing activity significantly when compared with the control. This study suggests that ME possesses an antidepressant without an anxiolytic-like effect. However, at high doses, the extract might show the sedative effect and alter other functions such as muscle strength, animal activity in the maze and pain response (Sattayasai et al., 2008).

CONCLUSION

This review presents some phytochemicals and detailed pharmacological information of *M. alba* L. The review of the pharmacological studies suggests that the medicinal uses of the plant in diabetes, hypertension, central nervous system (CNS) disorders, Hepatoprotective and cardiac diseases are scientifically valid. Besides, still there are options to investigate the unexplored potential of the plant based on its uses.

The knowledge of medicinal plants is species specific and restricted to a few individuals which differs from ancient system and due to lack of written documentation, many prime remedies are vanishing with generation. Further investigation of the plant can increase the isolation of the newer molecules which will be helpful for the study of the pharmacological activities from the plant, thus preventing the human and the economic losses in the environment.

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