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Review Article

White Mulberry (*Morus alba*): A Brief Phytochemical and Pharmacological Evaluations Account

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Abstract

Different plants are rich source of medicines. Since old days, Ayurveda and other disciplines reported the various pharmacological properties of naturally occurring plants against certain specific diseases. Currently, increasing health concern urged the researchers to revitalize the natural products and to alleviate the diseases without harming the body. In spite of medicinal uses of natural products, health supplements from natural products and their use in diet are gaining importance. Several bioactive constituents in natural products have the ability to protect from degenerative diseases and free radical production. The objective of this review is to unveil the phytochemistry, nutritional profile and pharmacologically active constituents of *Morus alba* L. The bioactive constituents isolated from *M. alba* such as leachianone and kuwanon G showed antibacterial activities and 1-deoxynojirimycin (DNJ) showed α- glycosidase inhibitors activity. Likewise, *M. alba* extract and its other compounds usually flavonoids have antioxidant properties by scavenging free radicals and protect many organs from oxidative stress. Anti HIV and chemo-protective activities have also been reported but further research may reveal their exact mode of actions.

Keywords: White mulberry; *Morus alba*; Phytochemistry; Therapeutic uses

Introduction

Conventional medicines show reliance on phytochemicals rich plants extracts to cure different maladies because medicines obtained from natural origin are considered to be less toxic and free from undesirable effects as compared to synthetic ones. Genus *Morus* (Mulberry) is an example that contains more than 150 species, *Morus alba* L. (white mulberry) is dominant specie among them (Srivastava *et al*., 2006). *M. alba* is monoecious, deciduous tree and is of medium size with a height of about 30 m and width of about 1.8 m, it is distributed throughout Asia, Africa, Europe and South and North America and found in wide range of tropical areas and in hilly areas of Himalayas at the height of 3300 m. It is reported that in Chinese medicine white mulberry has been widely used in medicine since 659 A.D and Chinese pharmacopoeia lists the root bark, stem, fruits and leaves as a constituent in medicinal preparations (Kumar and Chauhan, 2008). Other common name of white mulberry is silkworm mulberry and in Urdu, Persian and Hindi it is commonly called as shahtoot. Use of non-conventional feeds is gaining popularity in many developing countries of world because by feeding rich protein diet, the supply of amino acids to milking animals enhanced the milk production (Mohammadabadi and Chaji, 2012). *M. alba* leaves are used as fodder for silkworms and animals. In European countries it is grown for fruit production and it is also used as vegetable in different parts of the World, while in Japan mulberry leaves are used as tea and powder juice (Gerasopoulos and Stavroulakis, 1997; Ercisli and orhan, 2007; Katsube *et al*., 2009). The mulberry leaves are used as infusion in Asian countries most common in Japan and Korea. This is due the presence of steroids, flavonoids, amino acids, vitamins, triterpenes and other trace elements which show valuable effects (Deshmukh *et al*., 1993). Different plants have been reported for their biological activities such as anthelmintic, anti-parasitic (Badar *et al*., 2011; Babar *et al*., 2012) and anti-diarrheal properties (Jung *et al*., 2011). Because of its good therapeutic activity and low toxicity *M. alba* has been extensively used in conventional Chinese medicine (Li, 1998). *M. alba* is reported to have neuroprotective, skin tonic, antioxidant, anti-hyperglycemic, antibacterial, antihypertensive, and anti-hyperlipidemic activities (Nomura *et al*., 1980; Butt *et al*., 2008; Sun *et al*., 2011). The medicinal worth of various herbal or indigenous plants depends upon their chemical substances that generate a distinct physiological action in the human body (Gutierrez-Uribe *et al*., 2011). Several reports and studies proved that the pharmacological properties are due to polyphenolic compounds and

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secondary metabolites of medicinal plants and these may also be responsible for their total antioxidant potential (Elfalleh *et al*., 2011; Kaisoon *et al*., 2011). Wide range of medicinal activities have been credited to the different parts of the mulberry plant (Datta, 2000), the leaves of *M. alba* are dried and used in infusions in most of the Asian countries. The current review is intended to focus the pharmacological properties of *M. alba* in various diseases and disorders. Lastly we tried to draw some conclusion so that the researchers pay their attentions for further exploration of this natural plant.

Identification and Classification:

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Hamamelididae
Order	Urticales
Family	Moraceae
Genus	*Morus* L.
Species	*Morus alba* L.

Source: USDA, NRCS. 2012. The PLANTS Database (http://plants.usda.gov, 23 March 2012).

Nutritional Assessment

Carbohydrates, proteins, fibers, fats, minerals, vitamins and their precursors are present in significant amount (Butt *et al*., 2008). Ercisli and Orhan (2007) studied the chemical composition of *M. alba* fruits and reported that the weight of the fruit is 3.49 gram approximately and contains about 71.5 % moisture. *M. alba* have lower moisture contents and more fat contents (1.10%) then other species. Behenic acid (C22:0) and palmitoleic acid (C16:1) were present only in *M. alba* fruits (0.26% and 0.67%, respectively). *M. alba* has highest ascorbic acid contents (22.4 mg/100).

Similar study was conducted by Srivastava *et al*. (2006) to estimate the nutritional composition of mulberry leaves of six genotypes. This study reported that the fresh leaves contain moisturizer from 71.13 to 76.68%, protein from 4.72 to 9.96%, fat from 0.64 to 1.51% and carbohydrates from 8.01 to 13.42%. While in dried mulberry leaves the moisture content decreases and it ranged from 5.11 to 7.24%, from 15.31 to 30.91% for protein, from 2.09 to 4.93% for fat and from 9.70 to 29.64% for carbohydrates. Ascorbic acid was ranged from 160 to 280 mg/100 g in fresh mulberry leaves while in dried leaves its quantity decreased and ranged from 100 to 200 mg/100 g. Similarly in fresh leaves β-carotene was found to range from 10.00 to 14.688 mg/100 g, while in dried leaf powder its amount also ranged from 8.438 to 13.125 mg/100 g. The minerals content also varies in fresh and dried leaves and their composition is summarized in Table 1.

Phytochemistry of *M. alba*

M. alba leaves have antioxidant components, which includes rutin, isoquercitrin, astragalin and quercetin-3-(6-malonyl) glucoside among which quercetin - 3-(6-malonyl) glucoside is most abundant in dried mulberry leaf extract (Katsube *et al*., 2006). *M. alba* extracts have 13 known compounds. Koshihara *et al*. (1984) studied the selective inhibitory effect of caffeic acid on leukotriene biosynthesis and concluded that *M. alba* has high amount of caffeic acid, which selectively inhibits leukotriene biosynthesis, that appreciably play a vital role in various diseases like asthma, allergic reactions and inflammation.

The selection of the extraction solvent is very critical stage in order to extract the maximum quantity of active constituents because antioxidant components have varying polarities. Most efficient solution for the extraction of polyphenolic compound is 40% and 80% aqueous solution of ethanol and methanol (Suzuki *et al*., 2002). But the most suitable extraction solvent for total phenolic contents extraction in hazelnuts is 80% ethanol solution (Shahidi *et al*., 2007). Thabti *et al*. (2012) determined three more compounds in mulberry leaves which are quercetin 3-O-β-glucopyranoside-7-O-α-rhamnopyranoside, kaempferol-7-O-glucoside and quercetin-3-O-rhamnopyranoside-7-O-glucopyranoside. This study concluded that mulberry leaves are richest source of phytochemicals, which are beneficial for the health and can be used as vegetable. Complete range of polyphenolic compounds quantitatively determined is listed below in Table 2.

New Compound Isolated from *M. alba*

A new bioactive compound has been isolated from *M. alba* var. *multicaulis* Perro (Moraceae) along with 25 other known bioactive compounds (Yang *et al.,* 2011). The structure of these compounds was studied by spectroscopic methods, and this new compound was identified as, 3',5'-dihydroxy-6-methoxy-7-prenyl-2-arylbenzofuran. Table 3 elaborates the 26 bioactive compounds isolated and identified by Yang *et al*. (2011).

Pharmacological Activities of *M. alba*

Antimicrobial activity of *M. alba*: The use of antibiotics in excess is harmful for human body and also resistance occurred against harmful pathogens. So the demand of exploring natural compounds having activity against harmful pathogens is increasing day by day. Park *et al*. (2003) studied that mulberry extracts are rich in phytochemicals and have antimicrobial potential against harmful pathogens. In this study kuwanon G was separated from methanolic extract of *M. alba* it showed antimicrobial activity with minimum inhibitory concentration (MICs) of 8.0 µg/mL against *Streptococcus mutans* that is responsible for dental caries. This study also reveals that at

Table I: Mineral Contents in dried and fresh *Morus alba* leaves

	Contents in dried *Morus alba* L. leaves	Contents in fresh *Morus alba* L. leaves
Iron (mg/100)	19.00-35.72	4.70-10.36
Zinc (mg/100)	0.72-3.65	0.22-1.12
Calcium (mg/100)	786.66-2226.66	380-786

Source: Srivastava *et al*. (2007)

Table 2: Quantitative analysis of polyphenolic compounds present in *M. alba*

Compound		Amount (mg/100 g)
1	1-Caffeoylquinnic acid	58.42 - 58.90
2	Caffeic acid	1579.77 - 1588.25
3	5-Caffeoylquinnic acid	1380.80 - 1382.28
4	4-Caffeoylquinnic acid	124.61 - 124.93
5	Quercetin-3-O-rhamnoside -7-O-glucoside	272.60 - 273.06
6	Quercetin-3,7-D-O-β-D-glucopyranoside	137.949 - 137.991
7	Kaempferol-7-O-glucoside	211.432 - 211.488
8	Rutin	193.69 - 194.77
9	Quercetin-3-O-glucoside	972.466 - 972.494
10	Quercetin-3-O-(6-malonyl)-β -D-glucopyranoside	1258.58 - 1258.84
11	Quercetin-3-O-glucoside-7-O-rhamnoside	849.06 - 849.30
12	Kaempferol-3-Oglucopyranosyl-(1,6)-β –Dglucopyranoside	615.98 - 616.66
13	Kaempferol-3-O-(6-malonyl)glucoside	1332.91 - 1333.75
Total phenolic acids		3148.966 - 3148.994
Total flavonols		5846.30 - 5846.72
Total		8995.426 - 8995.546

Source: Thabti *et al*. (2012)

Table 3: Bioactive Compounds in *M. alba* var. *multicaulis*

1-	3',5'-dihydroxy-6-methoxy-7-prenyl-2-arylbenzofuran	14-	Morusin
		15-	Kuwanon E
		16-	Sanggenon F
2-	Moracin R	17-	Betulinic acid
3-	Moracin C	18-	Uvaol
4-	Moracin O	19-	Ursolic acid
5-	Moracin P	20-	β-sitosterol
6-	Artoindonesianin O	21-	Oxyresveratrol 2-O-β-D-glucopyranoside
7-	Moracin D	22-	Mulberroside A
8-	Alabafuran A	23-	Mulberroside B
9-	Mulberrofuran L	24-	5,7-dihydroxycoumarin 7-O-β-D-glucopyranoside
10-	Mulberrofuran Y		
11-	Kuwanon A	25-	5,7-dihydroxycoumarin 7-O-β-D-apiofuranosyl-(1→6)-O-β-D-glucopyranoside
12-	Kuwanon C		
13-	Kuwanon T	26-	Adenosine

Source: Yang *et al*. (2011)

the concentration of 20 µg/mL it totally inactivate *Streptococcus mutans* in 1 min and similarly kuwanon G also inhibits the proliferation of *Streptococcus sanguis*, *Porpyromonas gingivalis* and *Streptococcus sobrinus*. Similarly other phytochemicals present in *M. alba* also showed antimicrobial potential against various bacteria such as *Streptococcus faecalis*, *S. aureus*, *Mycobacterium smegmatis*, *B. subtilis*, and also against molds species. These antimicrobial activities were showed by bioactive molecules from mulberry bark, sanggenon B and D, Morusin and kuwanon C (Nomura *et al*., 1988). Leaves of mulberry also contains antimicrobial chemicals such as kuwanon C, mulberrofuran G and albanol B they show good antibacterial activity and their MIC range from 5 to 30 µg/ml (Nomura, 2001; Sohn *et al.*, 2004). Ayoola *et al.* (2011) evaluated the antibacterial and antifungal activity of phytoconstituents isolated from the aqueous and ethanolic (99.7% v/v) extract of *M. alba*. Antimicrobial potential was evaluated against different microbes by observing zone of inhibition and MICs. The study concluded that *M. alba* extracts can be able to treat bacterial and fungal infections and these activities are due to the presence of phytochemicals, minerals. Further conclusions reveals that cold water extract of plants showed low MIC as compared to hot water and ethanol extracts. Advance research can make us able to use these constituents for the treatment of infectious diseases.

Islam *et al*. (2008) evaluated the effect of compounds isolated from *M. alba* leaves against oral pathogens, commonly *Streptococcus mutan*. Compounds were purified by using silica gel chromatography and analyzed with different analytical techniques and by micro dilution method MICs were evaluated. The purified *M. alba* compound (1-deoxynojirimycin) showed 8-fold reduction of MIC against biofilm development of *S. mutans* than crude extract and it was revealed that 1-deoxynojirimycin inhibits the proliferation and formation of biofilm by S. mutans and can be used as therapeutic agent. A flavonoid compound leachianone G isolated from root bark of *M. alba* showed significant antiviral activity (IC50=1.6 µg/mL) against herpes simplex type 1 virus (HSV-1) (Du *et al*., 2003).

As *M. alba* is a rich source of phytochemical ingredients so there is need for further exploration of its antimicrobial agents. Researchers will focus on isolation, identification, purification of phytochemicals from *M. alba* and toxicological assessment of plant extracts. More research and effort is required to promote the commercial use of this plant as antimicrobial agent.

Antioxidant Activity of *M. alba*

M. alba is rich in polyphenolic compounds especially the flavonoids and among the flavonoids quercetin 3-(6-malonylglucoside) is most significant for antioxidant potential of mulberry plant (Butt *et al.*, 2008). The leaves of mulberry contains higher amount of quercetin which is responsible for reduction of oxidation process in vivo and in vitro (Enkhmaa *et al*., 2005; Katsube *et al*., 2006; Chen and Li, 2007; Iqbal *et al.*, 2012).

The ethanolic extract of *M. alba* leaves contains oxyresveratrol and 5,7-dihydroxycoumarin 7-methyl ether which scavenge superoxide and have antioxidant potential (Oh *et al*., 2002). Similarly aqueous extract of *M. alba* leaves showed highest antioxidant properties evaluated through ferric reducing/antioxidant power assay (Wattanapitayakul *et al*., 2005). Anthocyanin components from *M. alba* fruit were isolated and identified by Chen *et*

al. (2006) to check their antioxidant activity and reported that cyanidin 3-glucoside and cyanidin 3-rutinoside are of valuable importance as antioxidants. Mulberroside A is a major stilbene glycoside of *M. alba* and It showed inhibitory effects against $FeSO_4/H_2O_2$-induced lipid per oxidation in microsomes of rat and also found that Mulberroside A have scavenging effect on DPPH (1,1-diphenyl-2-picrylhydrazyl) radical (Chung *et al*., 2003). Rossetto *et al*. (2007) reported that the anthocyanin is present in mulberry extract and it is a natural colorant constituent for the plant. Anthocyanins showed antioxidant activity by scavenging the peroxyl radicals in trapping reaction.

Nephroprotective Effect of *M. alba*

M. alba has stilbene glycoside Mulberroside A and is successfully used for the management of gout and hyperuricemia in folk Chinese medicine. Wang *et al*. (2011) reported that mulberroside A shows uricosuric and nephroprotective effects. In hyperuricemia mice it decreases the serum level of urea nitrogen, creatinine, urinary N-acetyl- β-D-glucosaminidase action, albumin, β_2-microglobulin and enhanced the creatinine clearance. Further research is required in order to explore the nephroprotective constituents in *M. alba*.

We also conducted an experimental study on rabbits to evaluate the nephroprotective effect of *M. alba* against isoniazid induced nephrotoxicity. Parameters used for the analysis of nephrotoxicity were blood urea nitrogen and creatinine along with histopathological studies. It was reported that creatinine and urea clearance are the primary functions of glomerulus (Garba *et al*., 2011). Higher dose of isoniazid (100 mg/kg/day) produced significant nephrotoxicity in rabbits. Concomitant administration of hydro alcoholic extract of *M. alba* along with isoniazid significantly reduced the nephrotoxicity as evidenced by marked reduction in blood urea nitrogen and creatinine. Histological findings also proved the protective effect of *M. alba* against nephrotoxicity (Fig. 1) (Zafar, 2012).

Anti-HIV Activity of *M. alba*

Root bark of *M. alba* (San Baipi) a traditional Chinese medicine and is used for the management of cough, asthma and other such diseases. 14 compounds were isolated from *M. alba* and these compounds were tested against HIV. The Result showed that the ethanolic extract of San Baipi contains flavonoids like mulberrofuran D, mulberrofuran G, mulberrofuran K., morusin, and kwanon G, kwanon H and their derivatives. Only morusin, morusin 4´-glucoside and kuwanon H showed activity against HIV (Shi-De *et al*., 1995).

***M. alba* Natural Skin Tonic**

Recently much focus of the research is on the use natural products as skin whitening agents. Lee *et al*. (2002) studied the effect of methanolic extract of *M. alba* leaves on

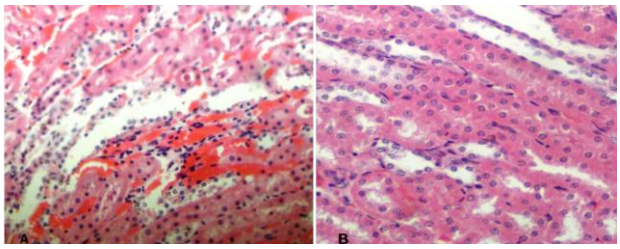

Fig. 1: Kidney of rabbit treated with INH 100 mg/kg body weight indicating nephrotoxicity (A) and INH 100 mg/Kg + *M. alba* 400 mg/kg body weight indicating nephroprotection (B) with daily oral administration for 28 days (H and E, x 40)

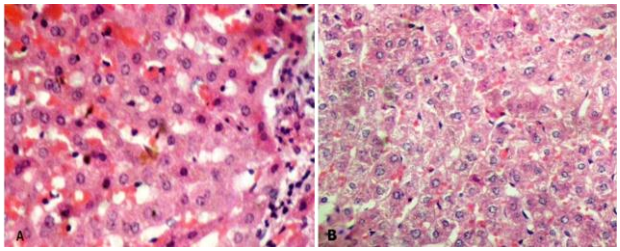

Fig. 2: Liver of rabbit treated with INH 100 mg/kg body weight indicating hepatotoxicity (A) and INH 100 mg/Kg + *M. alba* 400 mg/kg body weight indicating hepatoprotection (B) with daily oral administration for 28 days (H and E, x 40)

melanin biosynthesis. The melanin is responsible for hyperpigmentation. Tyrosine activity was inhibited by mulberroside F, isolated from extract. The result proposed that the isolated compound from *M. alba* have the potential as skin whitening agent. Chanda and Baravalia (2010) studied petroleum ether extract, toluene extract, ethyl acetate extract and methanol extract of various plants including *M. alba* for their microbial activity by using agar well diffusion method against bacteria and fungi causing skin diseases. Almost all solvent extracts of *M. alba* showed significant activity against bacteria and fungi. Therefore, knowledge of ayurvedic medicine should be supported by advance knowledge of science in order to isolate the active constituents from herbal resources.

Antihyperglycemic Activity of *M. alba*

Antihyperglycemic activity of mulberry leaves is due to the presence of trigonelline (Watanabe, 1958) and high fiber contents in mulberry leaves. Different parts of mulberry such as root and bark has been used for treatment in diabetes in conventional medicine (Bantle and Salma, 2006). *M. alba* leaves are used as ingredients in Thailand beverages and they are believed to enhance the health of diabetic patients. A polyhydroxylated piperidine alkaloid, 1-deoxynojirimycin (DNJ) isolated from leaves and root bark of *M. alba* have significant α- glycosidase inhibitors activity (Syvacy and

Sokmen, 2004; Oku *et al*., 2006). A study in humans indicates that oral administration of powder enriched with at a single dose of 0.8 and 1.2 g considerably inhibits the elevation of postprandial blood glucose and insulin secretion (Kimura *et al*., 2007). Examinations of the effect of ethanolic extract of *M. alba* are studied on oxidative damage, blood glucose, and glycation in streptozotocin-induced diabetic rats. Findings of this research supported that the use of *M. alba* leaves for long period of time have antioxidant, anti-hyperglycemic and anti-glycation effects in animal model (Naowaboot *et al*., 2009). Mulberry decreases the absorption of blood glucose (Lee *et al*., 2008). Further research on *M. alba* can reveal anti-hyperglycemic potential.

Anti-atherogenic Activity of *M. alba*

Atherosclerosis is caused by the increased production of free radicals by endothelial and vascular smooth muscles. Free radicals through various enzyme systems initiate the process of atherogenesis. Increase in the level of low density lipoprotein cholesterol (LDL-C) or more specifically hypercholesterolemia increases the free radical production and as a result elevates lipid peroxides (Harrison *et al*., 2003). Serum cholesterol level was inhibited by butanol extract of *M. alba* leaves, which prevent atherosclerosis (Doi *et al.*, 2001). Dietary use of *M. alba* leaves and their constituents was evaluated on the progress of atherosclerotic lesions in mice. The result suggested that atherosclerotic lesions were significantly decreased as compared with that of control groups (Enkhmaa *et al*., 2005). Similarly in hypercholesterolemic rats, the root barks 70% alcohol extract of *M. alba* inhibited the LDL induced atherogenic changes, LDL retention, oxidation, aggregation and production of lipid peroxides (El-Beshbishy *et al.*, 2006). Chen *et al.* (2005) studied that by feeding rabbits with *M. alba* water extract significantly reduced atherosclerosis in aorta and it was also revealed by histopathological studies.

Neuroprotective Effects of *M. alba*

Tian *et al*. (2005) reported that the neurodegeneration is mostly caused by free radicals production. Neurological disorders such as Parkinson's and Alzheimer's diseases have been due to the depletion of gamma amino butyric acid (GABA) in the brain. Kang *et al*. (2006) developed a process to increase the GABA level in *M. alba* leaves by various anaerobic treatments and they are subjected to *in vitro* and *in vivo* cerebral ischemia model. The results suggest that the anaerobic treatment of *M. alba* leaves increases the neuroprotection against *in vivo* cerebral ischemia as compared to *in vitro.* In further study it was investigated that cyanidin-3-O-β-d-glucopyranoside (C3G) was separated from mulberry fruit extract. C3G have neuroprotective effect on cerebral ischemic damage *in vivo* and PC12 cells exposed to hydrogen peroxide in vitro. Parkinson's disease is a common neurodegenerative disorder and is due to the loss of dopaminergic neurons in substantia nigra pars compacta. *In vitro* and *in vivo* studies of ethanolic extract of *M. alba* fruit was evaluated in Parkinsons's disease models. The result showed that the antioxidant and anti-apoptotic effects of *M. alba* significantly protected neurons from neurotoxins in *in vitro* and *in vivo* models (Kim *et al*., 2010). Alzheimer's disease is other common neurodegenerative disorder. The use of mulberry leaves reduced the risk of this disease and leaf extract of mulberry provides a significant source of treatment for Alzheimer's disease by inhibition of amyloid beta-peptide (1-42) fibril formation. As a result attenuation of the neurotoxicity induced by amyloid beta-peptide (1-42) was observed (Niidome *et al*., 2007). These studies suggested that *M. alba* or their isolated compounds can be used as neuroprotective agents for the treatment of neurodegenerative diseases.

Immunomodulatory Effects of *M. alba*

Immune system is the main regulatory system controlling homeostasis of the body and plays an important role in the progression of life from birth to death. The immune system can be protected and balanced by using immunostimulators (Awais and Akhtar, 2012). *M. alba* contains a higher quantity of flavonoids, especially anthocyanins and other active compounds which may plays an important role in enhancing the immunity. Kim *et al*. (2000) reported that polysaccharide separated from mulberry showed Immunomodulatory activity. In a study Immunomodulatory activity of aqueous extract of *M. alba* leaves was evaluated in wistar rats at dose of 200 and 400 mg/kg orally. Higher dose of extract (400 mg/kg) showed better immunomodulatory activity and *M. alba* extract initiate the innate or non-specific immune system and no effect on adaptive immune system (Venkatachalam *et al*., 2009). Similarly, the effect of methanolic extract of *M. alba* leaves was evaluated on immune system by various experimental models. The levels of serum immunoglobulin increased by *M. alba* extract and reduced the mortality in mice. *M. alba* L. significantly increased the circulating antibody titer, phagocytic index and a significant protection from cyclophosphamide induced neutropenia and enhanced the adhesion of neutrophils. Finally it was concluded that *M. alba* extract enhanced the humoral and cell mediated immunity in experimental animals models (Bharani *et al*., 2010). Focus should be on isolating the active constituents from leaves, root bark and other parts of *M. alba* and explore their immune-protective role.

***M. alba* Action against Cancer**

Cancer is one of the major causes of death in animals specially felines and canines. It was observed that longer the life of animals, the chance of exposure to carcinogenic agents increased. Because of high incidence of cancer, new studies are currently being performed with the aim of

finding better and safer therapeutic agents (Nardi *et al*., 2011).

Prenylated flavanone, 7, 2′, 4′, 6'-tetrahydoroxy-6-geranylflavanone separated from ethyl acetate extracts of *M. alba* root showed cytotoxic activity against hepatoma cells in rats with an IC_{50} of 52.8 mg/mL (Kofujita *et al*., 2004). Similarly, anthocyanins isolated from *M. alba* fruit showed inhibitory effect on invasion and migration of highly metastatic A549 human lung carcinoma cells in dose-dependent manner (Colonna *et al*., 2008; Martin-Moreno *et al*., 2008). Methanolic extract obtained from *M. alba* and its sub fractions obtained from aqueous, butanol and chloroform fractions blocked or inhibited the NO production and significantly reduced the formation of tumor necrosis factor-a (TNF-a) in macrophages, which were LPS activated RAW2647 (Choi and Hwang, 2005). Further evaluation and clinical trials may reveal the therapeutic potential of *M. alba* against cytotoxic cells, which may helps in finding a cheap and easily available source for treatment of cancer and decreasing invasiveness of cancerous cells.

Anti-hyperlipidemic Activity of *M. alba*

Mulberry leaves have the ability to be used as anti-hyperlipidemic agent due to the specific inhibitory effect of *M. alba* on the synthesis of fatty acids. Chen *et al*. (2005); El-Bebshbishy *et al.* (2006) have demonstrated such findings in experiments by using *M. alba* fruit and root bark. *M. alba* leaves are widely used in Brazil to safeguard the liver and to decrease the cholesterol and blood pressure. *M. alba* leaves aqueous extract was administered to hyperlipidemic rats by oral route with diet rich in cholesterol at the dose of 150 mg/kg/day for 14 days. Aqueous extract of *M. alba* lowered the plasma triglycerides level drastically. For that reason, the treatment not only reduced the plasma level of triglycerides but also repress development of liver damage in hyperlipidemic rats which supported the reality that the extracts of *M. alba* leaves have a great potential of use in traditional medicines and moreover their phytochemical studies should be carried out to isolate the active constituents (Zeni and Molin, 2010).

Hepato-protective Activity of *M. alba*

The liver is the major organ controlling all the biochemical pathways related to growth, supply of nutrients and energy provision. Substances that damage liver are known as hepatotoxins e.g. aflatoxin contaminated diet impaired the liver functions (Muhammad *et al*., 2012). Oh *et al.* (2002) reported that *M. alba* contains flavonoids, coumarine, and stilbene, which possess hepatoprotective activity. Similarly, Zeni and Molin (2010) reported that *M. alba* leaves aqueous extract protects the liver. The crude hydro alcoholic extract of *M. alba* has hepatoprotective effects in mice. For this purpose *M. alba* hydro alcoholic extract was studied against carbon tetrachloride (CCl_4) induced hepatotoxicity in mice. This research showed that the extract has the greatest power to capture the free radicals, which pose an important threat to many of the chronic liver disorders. The result of this study suggested that liver necrosis, tissue damage and vacuoles were significantly reduced in the mice group treated with *M. alba* so, its hydro-alcoholic extract declared as potent hepatoprotective (Kalantari *et al*., 2009). Hogade *et al*. (2010) studied the hepatoprotective potential of *M. alba* leaves extracts against hepatotoxicity induced by CCl_4. The results suggested that alcoholic extract and aqueous extract showed significant protective potential against the toxicity induced by CCl_4. However, the alcoholic extract showed noteworthy hepatoprotective effect, which was revealed by biochemical and histopathological parameters. Hussein *et al*. (2010) studied the liver protective effect of *M. alba* and *Calendula officinalis* extracts against CCl_4 induced toxicity in isolated rat hepatocytes. *M. alba* and *C. officinalis* extracts prominently reduced the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) and maintained the integrity of isolated hepatocytes. The study confirmed that these plants have significant hepatoprotective effects against hepatotoxicity induced by CCl_4.

We also conducted the similar studies to evaluate the hepatoprotective effect of hydroalcoholic extract of *M. alba* against hepatotoxicity induced by isoniazid in albino rabbits. Hydroalcoholic extract of *M. alba* proved efficient in reducing isoniazid-induced hepatotoxicity as evidenced by significant decrease in ALT and AST (Waheed, 2012). Histological findings have also indicated the protective effect of hydroalcoholic extract of plant against hepatotoxicity (Fig. 2).

Anti-stress Effect of *M. alba*

Supplementation with different nutrients and herbal preparations has been studied for adaptogenic activity during exposure to stressful conditions (Kenjale *et al*., 2007). *M. alba* is one of them and in Indian traditional medicine it is used as nervine tonic (Nadkarni, 1976). The activity of orally administered *M. alba* fruit extracts was evaluated during and after the physical exercise in rat and change in monoamine oxidase (MAO) activities was determined. The study concluded that *M. alba* adjust the MAO activities during exercise and promote the capability of physical activities and showed considerable anti-stress activity and enhanced the potential of physical activities (Hwang and Kim, 2004). Sattayasai *et al*. (2008) observed the effects of an aqueous extract of *M. alba* leaves green tea on mouse depression, anxiety, climbing activity and thermal response were evaluated. Rats were injected intra-peritonealy *M. alba* leaves green tea. After 30 min of injection rats were tested in experimental models. Finally the results suggests that *M. alba* leaves green tea showed an antidepressant activity and does not show anxiolytic effect

and at high doses the extract showed sedative activity to some extent. Nade *et al*. (2009) studied the adaptogenic potential of ethyl acetate-soluble fraction of methanol extract of *M. alba* roots in rats. Ethyl acetate soluble fraction of methanol extract of *M. alba* roots were administered before unpredictable foot shock for 21 days. The result of the study suggested that ethyl acetate soluble fraction of methanol extract of *M. alba* roots showed significant anti-stress potential. Similarly, Nade and Yadav (2010) designed a research to evaluate the anti-stress activity of *M. alba* in rats. Chronic stress was induced by restraining the rats inside a cylindrical plastic tube for 3 h daily for 10 days. The soluble fraction of *M. alba* made up of ethyl acetate at different doses were administered before production of stress. Chronic restraint stress causes cognitive dysfunction, distorted behavioral parameters, enhanced leucocytes count, superoxide dismutase (SOD), lipid peroxidation (LPO), glucose and corticosterone levels, with concomitant decrease in catalase (CAT) and glutathione reductase (GSH) activities. These observations suggested that *M. alba* have significant potential as an anti-stress agent and this study indicates that it can be used for the management of disorders induced by oxidative stress. By further exploration *M. alba* can be used as drugs alternative to conventional therapy and also health promoting supplement for the management of stress, dementia, depression and Parkinson's disease.

Conclusion

Due to the global trend towards improved quality of life there is significant demand for medicinal plant-based supplements from natural sources that have no contamination from synthetic fertilizers or chemicals and have lesser side effects. *M. alba* now a days has been investigated in various scientific instigations in order to explore its active constituents, which may have medicinal worth. It is a rich source of flavonoids and other compounds which showed antimicrobial potential and free radical scavenging activity. *M. alba* is used in traditional medicine and claimed to have kidney tonic, liver tonic, cardio-protective, skin whitening, anti-hyperglycemic, neuroprotective and anti-ulcer activities. Leaves of *M. alba* are rich in protein and widely used in food formulations and also have neuroprotective functions, can be used against neurodegenerative disorders such as Alzheimer and Parkinsons. While other useful effects like immune-modulation and chemo-protective properties need further exploration by scientists. Still researcher should pay attention in isolation and identification of active constituents and probe its medicinal worth and strengthen the claim of folk medicines.

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