

Review Article

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## The Mulberry, *Morus alba* (L.): The Medicinal Herbal Source for Human Health

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### ABSTRACT

Nutrient contents in the leaves of mulberry, *Morus alba* (L) made it to occupy the pace making place in the sericultural practices. The mulberry, *Morus alba* (L.) is native to eastern and central China. It became naturalized in Europe centuries ago. The tree was introduced into America for silkworm culture in early colonial times and naturalized and hybridized with the native red mulberry. The red or American mulberry is native to eastern United States from Massachusetts to Kansas and down to the Gulf coast. The black mulberry is native to western Asia and has been grown for its fruits in Europe since before Roman times. It is a flowering, fast growing, woody and perennial plant. Taxonomically, it belongs to the family: Moraceae. Mulberry, *Morus alba* (L.) gained attention since time immemorial. This is due to its pharmacological and economic value. Use of mulberry leaves in sericulture has been reported in the ancient Chinese literature and therefore well recognized. Therapeutic Significance of Mulberry, *Morus alba* (L.) have been depicted in the ancient literature through Ayurveda. Some of the ayurvedic therapeutic preparations use fruits, leaves, roots, bark or latex of mulberry, *Morus alba* (L.) to administer against various human diseases. The raw mulberry fruits, of about 100 g are able to provide 180 kJ (43 kcal), 44% of the Daily Value (DV) for vitamin C, and 14% of the DV for iron; and other nutrients. The health benefits of mulberry, *Morus alba* (L.) include their ability to improve digestion, lower cholesterol, help in weight loss, increase blood circulation, build bone tissues, and boost the immune system. The fruits of mulberry, *Morus alba* (L.) also helps prevent certain cancers, slow down the aging process, lower blood pressure, protect eyes, and improve the overall body metabolism. The present attempt is an overview of the major pharmacological properties of Mulberry, *Morus alba* (L.) along with major applications of phytochemicals purified from it.

#### Keywords

Antioxidants,  
Mulberry, *Morus alba* (L.), Cancer, diabetes, Deoxynojirimycin

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## Introduction

Herbal contents are serving a lot to orchestrate the progression of development of faculty of Medicine. Human being trusts effective and time-tested home remedies that have survived for several generations. Human being is turning towards the herbal supplements than ever before. The person living in a medicated nation does not like to take the risk of side effect induced prescription drugs. The society is now looking for alternative ways of preventing any diseases or ailments. The herbal preparation from medicinal plants is the one of the humanity's oldest and wealthy health care tools. The herbal formulations are serving as the basis of modern medicines, Ancient civilizations relied on herbs and medicinal plants for healing, as do many contemporary culture throughout the world. According to the World Health Organization, near about eighty percent of the population of the world continues to use complimentary therapies, a major part of which are derived from the plants like, mulberry, *Morus alba* (L.). The mulberries are the sweet, hanging fruits from a genus of deciduous trees that grow in a variety of temperate areas around the world. Thought to possibly have originated in China, they have spread throughout the world and are highly praised for their unique flavor and impressive composition of nutrients. In fact, most varieties found in different parts of the world are considered to be "native" from those areas, as they are widespread. The scientific name of mulberries varies depending on which species you are looking at, the most common types are *Morus australis* and *Morus nigra*, but there are other delicious varieties as well. In terms of appearance, the berries grow very fast when they are young but gradually slow as their color changes from white or green to pink or red, and eventually settling on dark purple or even black. The sweet or tart flavor makes

these berries ideal for sherbets, jams, jellies, fruit tarts, pies, wines, teas, and cordials. In certain areas of the world, the flavors of the mulberry varieties differ, but the American mulberry and the black mulberry are considered to have the most powerful flavor and are widely sought after. Interestingly, the mulberry tree has another important resource, besides providing people with delicious berries and that is its leaves. The mulberry leaves are also the only known food source for silkworms.

The mulberry, *Morus alba* (L.) is also recognized as white mulberry. It is a fast-growing, small to medium-sized mulberry tree which grows to 10–20 m tall. The species, *Morus alba* (L.) is native to northern China. It is widely cultivated and naturalized elsewhere (United States, Mexico, Australia, Kyrgyzstan, Argentina, etc.). The genus *Morus* contains more than 15 species of deciduous plants commonly called mulberry. The major ones include *Morus alba*, *Morus nigra*, *Morus rubra*, *Morus australis*, *Morus atropurpurea*, *Morus cathayana*, *Morus notabilis* and *Morus mesozygia*. These are economically important plant because the leaves are extensively used in sericulture. Mulberries are filled with nutrients that are important for our body, including iron, riboflavin, vitamin C, vitamin K, potassium, phosphorous, and calcium. They also contain a significant amount of dietary fiber and a wide range of organic compounds, including phytonutrients, zeaxanthin, resveratrol, anthocyanins, lutein, and various polyphenolic compounds. Apart from this, many nutritional benefits and medicinal values are attributed to this plant. The leaves contain high amount of protein and the nutritional scientists in India suggested the use of dry leaf powder for making parathas, one of the most popular Indian food items. In Korea and Japan the mulberry leaves and fruits are included in their functional foods,

used in the preparation of tea (Fig. 1 and 2) and ice creams. This plant has remarkable effects in lowering serum glucose and blood cholesterol levels enabling their use in traditional Chinese herbal and folk medicines. These properties are due to the presence of many bioactive components such as flavonoids, polyphenols, alkaloids, terpenoids, steroids etc. in this plant (Scrivastava, *et al.*, 2003; Andallu and Varadacharyulu, 2003; Asano, *et al.*, 2001). Different parts (root bark, stem bark, leaves and fruits) of the mulberry, *Morus alba* (L.) have been extensively investigated for their various health benefits, including antioxidative, hypolipidemic, antihyperglycemic, and antiatherogenic effects (Harauma *et al.*, 2007). The present review focuses on the antioxidant activity and medicinal properties of mulberry, *Morus alba* (L.) responsible for its therapeutic utilization, with special emphasis on major bioactive principles from its different parts. The parameters considered for the present attempt of review on therapeutic Significance of Mulberry, *Morus alba* (L.) include: Antioxidative Potentials of mulberry, *Morus alba* (L.); Antidiabetic Significance of mulberry, *Morus alba* (L.); The mulberry, *Morus alba* (L.) for cardiovascular diseases; Anticancer effects of mulberry, *Morus alba* (L.); Anti-inflammatory effects of mulberry, *Morus alba* (L.); The mulberry, *Morus alba* (L.) for neurological disorders; The mulberry, *Morus alba* (L.) for skin diseases; Hepatoprotective Potentials of mulberry, *Morus alba* (L.); The mulberry, *Morus alba* (L.) for gastrointestinal disorders and Antimicrobial effects of mulberry, *Morus alba* (L.).

### **Antioxidative potentials of mulberry, *Morus alba* (L.)**

Presence of wide array of phytochemicals in different parts accounts for the antioxidative

potential of mulberry, *Morus alba* (L.). The fruits of mulberry, *Morus alba* (L.) are considered as nutritious food. This is because, the fruits of mulberry, *Morus alba* (L.) contain flavonoids and polyphenols. The most important flavonoids and polyphenols identified from mulberry, *Morus alba* (L.) are apigenin, luteolin, quercetin, morin, caffeic acid, gallic acid, rutin, umbelliferone, chlorogenic acid and kaempferol (Arfan, *et al.*, 2012 and Chu, *et al.*, 2006). The compounds like maclurin, rutin, isoquercitrin, resveratrol and morin belong to the twigs and root bark of mulberry, *Morus alba* (L.) (Chang, *et al.*, 2011). The fruits of mulberry, *Morus alba* (L.) contains essential fatty acids like palmitic, oleic and linoleic acids which are important for cell membrane formation, proper development and functioning of nervous system, production of eicosanoids and many inflammatory responses (Ercisli and Orhan, 2007). *Morus cathayana* (L.) is one more species of mulberry. This *Morus cathayana* (L.) is a deciduous tree usually found in secondary forest and scrubland. The tree of mulberry, *Morus cathayana* (L.) reaches a height of up to 15 metres (49 feet). It use to flower from May to June. It produces edible berries and its leaves are made into a tea. The phytochemical investigation of the stem bark of mulberry, *Morus cathayana* (L.) led to the isolation and identification of cathayanin and various cathayanons (Ni, *et al.*, 2010). Few arylbenzofurans with antioxidant and anti-inflammatory activities were reported from *M. wittiorum* (Tan, *et al.*, 2010). HPLC coupled with UV absorption detection lead to the identification of five important stilbene glycosides from mulberry, *Morus alba* (L.) (Piao, *et al.*, 2011). Benzokuwanon E, hydroxymorusin, dicyclokuwanon EA, and dicyclokuwanon EB are the important flavonoids isolated from *Morus australis* (L.) and their structures were elucidated on the basis of UV, IR, MS, NMR, and CD spectral data (Zheng, *et al.*, 2012).

The aqueous extractives the leaves of mulberry, *Morus alba* (L.), prepared at high temperature was reported to contain four important flavonols, quercetin-3- $\beta$ -D-glucose, quercetin-3-O-glucose-6'-acetate, rutin and quercetin (Kim and Jang, 2011). The lupeol type pentacyclic triterpenoids separated from the stem bark of mulberry, *Morus alba* (L.) include: moruslupenoic acid A, moruslupenoic acid B and moruslanosteryl acetate (Ali and Ali, 2012). The aqueous methanolic extract of the root bark of mulberry, *Morus alba* (L.) yields the compound "Moran 20K". The Moran 20K is a glycoprotein with antioxidant antidiabetic activity (Kim, 1999). 1-deoxynojirimycin (DNJ), resveratrol, oxyresveratrol, cyanidin-3-O-beta-glucoside (Cy-3-glu), cyanidin-3-O-beta-rutinoside (Cy-3-rut), and rutin were also reported in different species of mulberry (Song, *et al.*, 2009). The compounds like sanggenol, kuwanon, moracin, mulberrofuran, mulberroside, 1-deoxynojirimycin, 2-O-alpha-Dgalactopyranosyl-1-deoxynojirimycin, fagomine, betulinic acid, ursolic acid and beta-sitosterol are the important chemical constituents of the root bark of mulberry, *Morus atropurpurea* (L.). Kumar, *et al.*, 2008 and Butt, *et al.*, (2008) the literature on the major pharmacologically important compounds from mulberry, *Morus alba* (L.) and other species of mulberry. Vitthalrao B. Khyade, *et al.*, (2013, 2014, 2015, 2015, 2018) assessed the capabilities of moracin as antioxidant and reported it as ideal herbal compound to prevent oxidative stress. The potential regarding antioxidant activity of Moracin, the novel compound belong to mulberry was assessed through the use of hydrogen peroxide induced stress in skin fibroblast cell line culture (AH927) by Vitthalrao B. Khyade *et al.*, (2018). The results of this attempt showed that the Moracin offers protection against oxidative stress. And cell viability was found restored to that of control on pre-incubation with the

Moracin. The fibroblasts pre-incubated with Moracin had significantly lower levels of catalase; lactate dehydrogenase and malondialdehyde activity when compared to untreated ones. The acetone-soluble (and water soluble too) Moracin, from a natural source, the fruits of mulberry, *Morus alba* (L.), serve as ideal molecule to prevent oxidative stress.

### **Antidiabetic significance of mulberry, *Morus alba* (L.)**

The Diabetes mellitus is a group of metabolic disorders. It is characterized by high blood sugar (glucose) levels. This high blood sugar (glucose) levels is in response to the defects in insulin secretion, or its action, or both. The disease diabetes mellitus was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Increased levels of blood glucose (which may also called as hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, in healthy body, the blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level by promoting the uptake of glucose into body cells. In diabetic patients, the absence of insufficient production of or lack of response to insulin causes hyperglycemia. The Diabetes mellitus is thus characterized by sustained hyperglycemia. It is associated with many secondary complications in the body metabolism. The secondary complications through diabetes mellitus include: formation of free radicals and non enzymatic glycosylated end products. This situation is responsible for higher oxidative stress and vascular complications (Ahmed, 2000; Baynes and Thorpe, 2000). Naowaboot *et al.*,



(2009) reported the antihyperglycemic, antioxidant and antiglycation activities of extractives of leaves of mulberry, *Morus alba* (L.) in streptozotocin induced chronic diabetic rats. The leaves of mulberry, *Morus alba* (L.) are one of the important herbal medicines used for the treatment of hyperglycemia. It was proved by experiments in animal models that mulberry leaf extract possess antihyperglycemic, antioxidant and antiglycation activities (Naowaboot, *et al.*, 2009). The extractive of the leaves of mulberry, *Morus alba* (L.) is reported as effective in modulating the nitric oxide synthase expression in the hypothalamus of streptozotocin treated rats (Jang, *et al.*, 2002). The red mulberry, *Morus rubra* (L.) is a species of mulberry native to eastern and central North America. The leaf extractives of this red mulberry, *Morus rubra* (L.) exerts its antidiabetic activity in streptozotocin induced diabetic rats by decreasing the fasting glucose levels, glycosylated haemoglobin and increasing the plasma insulin and C-peptide levels (Sharma, *et al.*, 2010). The credit of antidiabetic activity of mulberry, *Morus alba* (L.) goes to its novel compound: 1-Deoxynojirimycin (DNJ). This 1-Deoxynojirimycin (DNJ) has been shown to inhibit intestinal  $\alpha$ -glucosidases, which results in reduction of blood glucose (Hansawasdi, *et al.*, 2006). According to Li, *et al.*, (2011), a hybrid of 1-Deoxynojirimycin (DNJ) and a polysaccharide helps in regulating the expression of the hepatic gluconeogenic enzymes, glucokinase, PEP carboxykinase and glucose 6-phosphatase. The polysaccharide in this mixture is able to protect pancreatic islets from alloxan induced damage, repair the destroyed pancreatic islets, upregulate the PDX-1, insulin-1 and insulin-2 expression in pancreas and normal secretion of insulin in serum. Taniguchi, *et al.*, (1998) fagomine contents in the leaves of mulberry, *Morus alba* (L.). Fagomine of mulberry leaves is capable of inducing insulin secretion in

isolated rat islet cells. In patients with type 2 diabetes, mulberry treatment caused an improvement in glycemic control and fall in VLDL production. Also it decreased the lipid peroxidation in blood, urine and RBC membrane (Andallu *et al.*, 2001). The moracin M; steppogenin-4'-O- $\beta$ -D-glucosiade and mullberroside-A were also isolated from the root bark of mulberry, *Morus alba* (L.). All the three flavones (moracin M; steppogenin-4'-O- $\beta$ -D-glucosiade and mullberroside-A) exhibited hypoglycemic effect in alloxan induced diabetic mice (Zhang, *et al.*, 2009). There is important role of  $\alpha$ -amylase, the key enzyme catalyzes the initial step in the hydrolysis of starch to smaller oligosaccharides. Retardation of starch digestion by inhibition of  $\alpha$ -amylase, the key enzyme catalyzes the initial step in the hydrolysis of starch to smaller oligosaccharides plays a key role in the control of diabetes. The extractives of leaves of mulberry, *Morus alba* (L.) rich in tannins, flavonoids, cardiac glycosides and saponins exhibit significant  $\alpha$ -amylase inhibitory activity (Sudha *et al.*, 2011).

The insulin resistance and low grade chronic inflammatory status are the distinguishing features of type 2 diabetes. The secondary complication associated with type 2 diabetes is the development of cardiovascular diseases. Type 2 diabetic related resistance of insulin depends both on glucose metabolism and fatty acid metabolism (Haffner, 1991). Improvement in insulin resistance has been suggested as an effective way to prevent life style related type 2 diabetes and vascular complications. Repeated ingestion of extractives of leaves of mulberry, *Morus alba* (L.) reduces the insulin resistance in high fat fed KK-Ay mice (Tanabe, *et al.*, 2011). Kim, *et al.*, (2012) reported improvement in the markers of inflammation and insulin resistance in experimental animal models through the long term provision of extractives

of leaves of mulberry, *Morus alba* (L.). The circulating oxidized low density lipoproteins (LDL) was also improved in the treated group, which is often elevated in type 2 diabetes. The extractives of leaves of mulberry, *Morus alba* (L.) increases the rate of glucose uptake by a direct enhancement of insulin independent glucose transport in skeletal muscle. 5'-AMP-activated protein kinase (AMPK) is the major signaling intermediary in the exercise-stimulated insulin independent glucose transport in skeletal muscle (Musi, *et al.*, 2006). The skeletal muscle AMPK is also implicated in a variety of antidiabetic properties of exercise, including glucose transporter 4 (GLUT4) expression, glycogen regulation, fatty acid oxidation and enhanced insulin sensitivity. Mulberry leaf extract increases the activity of both AMPK  $\alpha$  1 and 2 in skeletal muscles and is associated with insulin independent glucose transport without change in the energy status of the muscle and reduces the risk of type 2 diabetes (Ma, *et al.*, 2009). Decrease in adipogenesis lead to limited storage sites for free fatty acids cause increase in plasma free fatty acids. This increase in circulating free fatty acids result in fat deposition in muscle and liver causing insulin resistance and type 2 diabetes mellitus. Adiponectin is a member of the adipokine family is induced during adipocyte differentiation. Circulating levels of adiponectin will be low in patients having obesity and type 2 diabetes (Nadler, *et al.*, 2000).

The extractives of leaves of mulberry, *Morus alba* (L.) stimulates differentiation of 3T3-L1 preadipocytes into adipocytes by increasing the expression of adipogenic genes and improve the secretion of adiponectin and insulin sensitivity. This mechanism of action is similar to that of the thiazolidinediones, a class of insulin sensitizing drugs used to treat type 2 diabetes (Naowaboot *et al.*, 2012).

Reduction in the fasting blood sugar, normalization of liver enzymes level and improvement in the lipid profile are reported in the diabetic rats treated with the extractives of leaves of mulberry, *Morus alba* (L.) (Vitthalrao B. Khyade, 2014).

The treatment of diabetic rats using the decoction leaves of Mulberry, *Morus alba* (L.) (20 g/L) is reported to decrease the blood glucose levels, to inhibit hepatic glycogen loss, and to prevent potential histopathological alterations in the pancreas and kidneys. The provision of leaf decoction of Mulberry, *Morus alba* (L.) (20 g/L) was found to be able to regulate the altered metabolic processes. The results suggest that Mulberry, *Morus alba* (L.) leaf decoction (20g/L) is useful for diabetes mellitus management (Vitthalrao B. Khyade, 2018). Mulberry, *Morus alba* (L.) should be explored as medicinal plant to be used to control the diabetes. Given a reasonable likelihood that medicinal plants with a long history of human use will ultimately yield novel drug prototypes, systematic and intensive search in plants for new drugs to treat Type 2 diabetes mellitus seem to be of a great utility. This approach seems likely to increase the chances for discovering new drugs for the management of diabetes mellitus.

### **The mulberry, *Morus alba* (L.) for cardiovascular diseases**

The mulberry, *Morus alba* (L.) has been widely used to prevent and to treat symptoms associated with cardiovascular disease for over a millennium in eastern countries. Aqueous preparations of mulberry, *Morus alba* (L.) were used in the herbal prescriptions by Chinese people to reduce blood pressure. The leaf extractives of the mulberry, *Morus alba* (L.) shown to reduce hypertension in rodents and decreases serum cholesterol and prevent atherosclerosis (Doi, *et al.*, 2000 and

Oh, *et al.*, 2007). The ethyl acetate extractives of mulberry, *Morus alba* (L) has dual vasoactive effects. The relaxation was mediated by inhibition of voltage- and receptor dependent Ca<sup>2+</sup> channels in vascular smooth muscle cells, while the contraction occurred *via* activation of ryanodine receptors in the sarcoplasmic reticulum (Xia, *et al.*, 2008). The deoxyribonucleic acid (DNA) micro array analysis were used to investigate gene expression in the livers of hypertriglyceridemic rats treated with mulberry leaves to elucidate the mechanism behind the lipid lowering effect of mulberry. Dietary supplementation increased protein expression of the Carnitine Palmitoyltransferase 1A (CPT1A); Acyl-CoA Oxidase 2 (ACOX2); phytanoyl-CoA hydroxylase (PHYH) and the activity of acyl-CoA oxidase / dehydrogenase, the rate limiting enzymes of fatty acid oxidation. The genes upregulated by mulberry included the following peroxisome proliferator-activated receptor alpha (PPAR alpha) and or peroxisome proliferator-activated receptor delta (PPAR delta) targets and many of them are involved in fatty acid oxidation. Angiotensin-like 3 (also known as ANGPTL3), is a protein that in humans is encoded by the *ANGPTL3* gene (Conklin, *et al.*, 1999). Mulberry induced down regulation of this *ANGPTL3* results in the activation of lipoprotein lipase and enhanced triglyceride hydrolysis. Mulberry administration also upregulated the Glycerol Kinase gene (*Gyk* gene) and caused a reduction in the plasma non esterified fatty acid level. The Stearoyl-CoA desaturase gene (*Scd* gene) is the gene involved in lipogenesis and this gene was down regulated after treatment with mulberry which inhibits lipogenesis and facilitates fatty acid oxidation (Kobayashi, *et al.*, 2010). *Morus Bombycis* is an extract found in mulberries that is often used in cosmetics due to the presence of arbutin, a hydroquinone derivative isolated from the leaves of the

bearberry shrub, cranberry, blueberry, some mushrooms, and most types of pears. *Morus Bombycis*' arbutin can potentially prevent melanin production, Therefore, naturally lightening skin and creating a more youthful appearance (Source). *Morus bombycis* is also high in antioxidants, and although this property has made it a popular inclusion in the treatment of liver disease and other internal ailments, it is also an effective free radical scavenger. *M. bombycis* root extract exhibited strong anti-lipase activity, with an IC<sub>50</sub> value of 2.07µg/ ml in fully differentiated 3T3-L1 adipocytes and adipose tissues. The extract increased lipolytic effects such as decreased intracellular triglyceride and the release of glycerol. Moreover it inhibited phosphodiesterase activity in a dose dependent manner (Kim *et al.*, 2010). So it does have pharmacological applications in metabolic disorders such as obesity. DNJ present in mulberry leaf extract helps in increasing serum adiponectin level, stimulated AMP activated protein kinase to activate β-oxidation which inhibits lipid accumulation in liver (Kim, *et al.*, 2010). Mulberry water extract inhibited acetyl coenzyme A carboxylase activities by stimulating AMPK and attenuated the expression of sterol regulatory element binding protein 1 and its target molecules such as fatty acid synthase. In contrast, the lipolytic enzyme expressions of PPAR gamma and carnitine palmitoyltransferase1 were increased (Ou, *et al.*, 2011) (Fig. 3).

Continuous for 12 weeks of provision of the herbal capsules of 1- Deoxyojirimycin (DNJ) rich mulberry leaf extractives for humans reported a modest decrease in serum triglyceride levels and beneficial changes in lipid profile without any side effects (Kojima, *et al.*, 2010). Administration of freeze dried powder of fruits of the mulberry, *Morus alba* (L.) to rats resulted in a significant decrease in serum and liver triglyceride, total cholesterol,

serum low-density lipoprotein (LDL) and decrease in atherogenic index. Also an increase in serum high-density lipoprotein (HDL) level, Red Blood Corpuscles (RBC) and liver superoxide dismutase (SOD) level and blood glutathione peroxidase level was observed. The thiobarbituric acid content of serum and liver was reduced indicating the low level of lipid peroxidation (Yang, *et al.*, 2010). Mulberry leaf powder can preserve the cardiac function in experimental autoimmune myocarditis by modulating oxidative stress induced MAPK activation and further afford protection against endoplasmic reticulum stress mediated apoptosis. It significantly decreased oxidative stress, myocyte apoptosis, cellular infiltration, cardiac fibrosis, mast cell density, myocardial levels of sarco/endo plasmic reticulum Ca<sup>2+</sup>-ATPase2, p22phox, receptor for advanced glycation end products, phosphor p38 mitogen activated protein kinase, phospho-c-Jun-NH<sub>2</sub>-terminal protein kinase, glucose regulated protein78, caspase12 and osteopontin levels (Arumugam, *et al.*, 2013). Morusinol extracted from *M.alba* root bark significantly inhibited collagen and arachidonic acid induced platelet aggregation and TXB<sub>2</sub> formation in cultured platelets. So it is effective in inhibiting arterial thrombosis *in vivo* due to antiplatelet activity and exerts beneficial effects on transient ischemic attacks or stroke via modulation of platelet activation (Lee, *et al.*, 2012). Some isoprenylated flavonoids with adipogenesis promoting activity were purified from *M. nigra* and *M. notabilis* (Hu, *et al.*, 2011 and Hu, *et al.*, 2011). The extractives of mulberry, *Morus alba* (L.) increases the vascular smooth muscle cell migration in a dose dependent manner by inhibiting the activities of MMP-2 and 9, phosphorylation of FAK, protein expression of small GTPases (c-Raf, Ras, Rac1, Cdc42, and RhoA) and NF-kappaB expression (Chan, *et al.*, 2009). Also the extractives of leaves of mulberry, *Morus alba*

(L.) helps in inhibiting the vascular smooth muscle proliferation by the upregulation of p53 and inhibition of cyclin dependent kinase (Chan, *et al.*, 2010). The high levels of iron content in mulberries can significantly boost the production of red blood cells. This means that the body will increase its distribution of oxygen to important tissues and organs, thereby helping to boost metabolism and optimize the functionality of those systems. Resveratrol is a very important flavonoid that directly affects the functioning of certain mechanisms in blood vessels, primarily making them less prone to damage by angiotensin, which can cause blood vessel constriction. In fact, resveratrol increases the production of nitric oxide, which is a vasodilator. This means that it relaxes blood vessels and reduces chances of blood clot formation and subsequent heart issues like strokes or heart attacks. Resveratrol is found in many dark-skinned berries like mulberries. Because mulberries are high in vitamin C and flavanoids, they can also help prevent cold and flu-like symptoms, and even treat hepatitis. They are a wonderful dietary addition for post-operative patients, too, since they can speed up recovery via improved blood circulation.

#### **Anticancer effects of mulberry, *Morus alba* (L.)**

Cancer is a serious public health problem world wide. Most of the natural compounds targets inflammatory pathways and immune modulation for the prevention and treatment of cancer. Mulberry also contains several anticancer compounds. *M. fructus* fruit extract induces cancer cell death *in vitro* and *in vivo*. The *in vitro* effect is due the cell death in an ROS dependent mitochondrial apoptotic pathway (Jeong, *et al.*, 2010). Phenolic compounds from mulberry, *Morus alba* (L.) induces *in vitro* anticancer activity in hepatoma cells by cell cycle arrest at G<sub>2</sub>-M



phase and inhibition of topoisomerase II activity (Naowaratwattana, *et al.*, 2010). Albanol A (also called as Mulberrofuran G) is the bio-active compound isolated from the root bark of mulberry, *Morus alba* (L.). This Albanol A was found inducing potent cytotoxicity (IC<sub>50</sub> 1.7mM) in HL60 cells (Human Leucemia Cell line) through inhibition of topoisomerase II activity (IC<sub>50</sub> 22.8mM). In addition, it induced early apoptosis through cell death receptor pathway and mitochondrial pathway, observed by membrane phospholipid exposure, reduced levels of pro caspase3, 8 and 9 and increased levels of cleaved caspase 3, 8 and 9 and increased bax/BCI2 ratio (Kikuchi, *et al.*, 2010). The anticancer activity of the essential oil separated from mulberry, *Morus rotundiloba* Koidz was studied in human larynx epidermoid carcinoma (Hep2) and human colon adenocarcinoma (SW620) cell lines with African green monkey kidney (Vero) cell line as a control. The oil at 0.1-100 µg/ml had no effect on Vero cell viability. The median lethal concentration (LC<sub>50</sub>) of the oil on the cytotoxicity of Hep2, SW620 and Vero were 70, 120 and 280 µg/ml respectively (Patharakorn, *et al.*, 2010). Resveratrol, purified from the methanol extract of *M. alba* showed heparinase inhibition and antimetastatic effects on murine B16 melanoma cells (Ahn, 2006). The mulberry, *Morus alba* (L.) is a rich source of prenylated cytotoxic flavonoids such as sanggenon J and K, cyclomorusin, morusin, atalantoflavone, kaempferol etc. Henrietta Lacks (August 1, 1920 – October 4, 1951) was an African-American woman whose cancer cells are the source of the HeLa cell line, the first immortalized cell line and one of the most important cell lines in medical research. An immortalized cell line will reproduce indefinitely under specific conditions, and the HeLa cell line continues to be a source of invaluable medical data to the present day. The morusin is the most

potent among them. The morusin is with an IC<sub>50</sub> value of 0.64 µM against HeLa cells (Dat *et al.*, 2010). New 2-arylbenzofuran derivatives (namely moracins of different structure from mulberry, *Morus alba* (L.) and wittifurans from *Morus wittiorum*) with potent cytotoxic activity against different human cancer cell lines were identified recently (Yang, *et al.*, 2010 and Tan, *et al.*, 2012). A new galactose binding lectin was also purified from *M. alba* leaves with cytotoxic activity on human breast cancer (IC<sub>50</sub>-8.5 µg) and colon cancer cells (IC<sub>50</sub>-16 µg) (Deepa and Priya, 2012) (Fig. 4).

The anthocyanins are a group of phenolic compounds with beneficial effects in reducing the risk of cardiovascular diseases and cancer because of its antioxidant, anti-inflammatory and chemopreventive properties (Middleton, *et al.*, 2000). Cyanidin 3-rutinoside and cyanidin 3-glucoside are the two anthocyanins present in mulberry, *Morus alba* (L.). They have strong anticancer properties. They have shown to be inhibiting the invasion and migration of human lung cancer A549 cells by downregulating the expression of MMP-2 and urokinase plasminogen activator and enhances the expression of TIMP-2 and plasminogen activator inhibitor. Also an inhibition of the activation of NF-kappa B and c-jun was also observed in this case (Chen, *et al.*, 2006). The osajin is a prenylated isoflavone isolated from the fruit of *Maclura pomifera* (L.). The tree of *Maclura pomifera* (L.) and a tree of mulberry, *Morus alba* (L.), both belong to one and the same family (Moraceae). It exerts multiple effects such as loss of mitochondrial transmembrane potential, release of cytochrome C, expression of Fas ligand, suppression of glucose regulated protein 78 and activation of various caspases and proapoptotic proteins in human nasopharyngeal carcinoma cells. So osajin induced apoptosis include extrinsic death receptor pathway and intrinsic pathways

relying on mitochondria and endoplasmic reticulum (Huang, *et al.*, 2011). Chalcones, a group of aromatic enones from plants, form the central core of a number of biologically important compounds. Investigation on ethanol extract of the leaves of *M. alba* L. yielded two new chalcone derivatives, morachalcone B and C with potent cytotoxic effects (Yang, *et al.*, 2010). Flavonoids such as sanggenol L, sanggenol M and different types of mulberrofurans with cytotoxic effects were also purified from *M. mongolica* (Shi, *et al.*, 2001). Between the high content of anthocyanins, vitamin C, vitamin A, and various other polyphenolic and phytonutrient compounds, mulberries are absolutely packed with antioxidants. Antioxidants are the main line of defense against free radicals, which form a dangerous by-product of cellular metabolism and can damage healthy cells, causing them to mutate into cancerous ones. The diverse range of antioxidants found in mulberries means that they can neutralize these free radicals quickly before too much damage is done.

### **Anti-inflammatory effects of mulberry, *Morus alba* (L.) (Fig. 5)**

Mulberry plants have a long history in traditional medicine as anti-inflammatory agents. The root epidermis of mulberry, *Morus alba* (L.) shown to have anti-inflammatory effects (Wang, *et al.*, 2002). The leaves of mulberry, *Morus alba* (L.) have diaphoretic and emollient effects and are used for making a decoction that can be used as a gargle that throat inflammation. Butanol extract of mulberry, *Morus alba* (L.) significantly reduced LPS-induced PGE2 production, TNF-alpha and COX-2 expression in RAW264.7 macrophages (Choi, *et al.*, 2005). Methanol extract of mulberry, *Morus alba* (L.) contains compounds with inducible nitric oxide synthase (iNOS) inhibitory activity which can attribute to its

anti-inflammatory properties (Hong, *et al.*, 2002). It exerts antiasthmatic effect in experimental mouse model via enhancement of CD4+CD25+Foxp3+ regulatory T cells and inhibition of Th2 cytokines (Kim, *et al.*, 2011). The extract of *M. bombycis* has antiinflammatory and inhibitory effect on collagen induced arthritis. It acts by decreasing the infiltration of immune cells, synovial hyperplasia, cartilage destruction and bone erosion. The mRNA levels of MMP1/3, inflammatory cytokines and chemokines were significantly suppressed, number of osteoclasts were reduced and activation of NF-kappaB and Ap-1 were observed on treatment with the extract (Kim, *et al.*, 2011). The extractives of leaves of mulberry, *Morus nigra* (L.) and extractives of fruits of mulberry, *Morus ihou* Koidz are reported for capable of reducing the carrageenan-induced paw edema as well as fibrovascular tissue growth induced by s.c. cotton pellet implantation in animal models indicating its anti-inflammatory property (Kim, *et al.*, 2006 and Padilha, *et al.*, 2010). The cudraflavone B is a prenylated flavonoid found in large amounts in the roots of mulberry, *Morus alba* (L.) is reported to cause a significant inhibition of inflammatory mediators in selected *in vitro* models. It was a potent inhibitor of Tumor Necrosis Factor – alpha (TNF alpha) by blocking the translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) from the cytoplasm to the nucleus. The nuclear factor kappa-light-chain-enhancer of activated B cells NF-kB activity reduction resulted in the inhibition of cyclooxygenase 2 (COX-2) gene expression also [74]. (Hosek, *et al.*, 2011). The anti-inflammatory compound wittifuran I was purified from the ethanolic extract of stem bark of mulberry, *Morus wittiorum* (L.) (Tan, *et al.*, 2012). Another compound resveratrol from *M. alba* inhibits IL-8 secretion by blocking mitogen-activated protein kinase (MAPK) phosphorylation and nuclear factor

kappa-light-chain-enhancer of activated B cells (NF-kappaB) activation in lipopolysaccharide (LPS) induced human monocytic cell line THP-1 (Oh, *et al.*, 2009). Sanggenon C and O, two Diels-Alder type adducts isolated from *M. alba*, inhibit NO production through the iNOS induction and activation of nuclear factor (NF-kB) in LPS-induced RAW264.7 cells indicating its anti-inflammatory potential (Dat, *et al.*, 2012). Several arybenzofurans (moracins and mulberrofurans of different types), prenylated flavonoids (kuwanons, morusin, sanggenon F, betunilic acid etc.) from *M. alba* var. *multicaulis* Perro showed significant inhibitory activity towards the differentiation of 3T3-L1 adipocytes and inhibition in NO production in RAW264.7 cells (Yang, *et al.*, 2011). Phytochemical fractionation of the methanol extract of *M. alba* root bark lead to the identification of two chalcone derived Diels Alder adducts, kuwanon J trimethylester and kuwanon R with inhibitory effect on NFkB with IC50 value of 4.65 and 7.38  $\mu$ M respectively (Fung, *et al.*, 2012). Inhibitors of phosphodiesterase -4 (PDE4) enzymes have therapeutic applications as anti-inflammatory agent because inhibition of PDE-4 will lead to the accumulation of cAMP and thus attenuated inflammatory responses in various cell types. Molecular docking studies have shown that moracin M from *M. alba* can inhibit the activity of a variety of PDE-4 enzymes (Chen, *et al.*, 2012).

### **The mulberry, *Morus alba* (L.) for neurological disorders**

Unlike beneficial effect of mulberry in treating diabetes, cardiovascular disease, cancer etc., but its effects on neurological disorders are less studied. The neurotoxicity in Alzheimers disease (AD) is associated with the accumulation of amyloid beta-peptides that forms as a plaque in brain. The methanol extract of mulberry leaves contain compounds

such kaempferol -3-O-glucoside, and kaempferol -3-O-(6-malonyl) glucoside which inhibits the formation of amyloid beta-peptide fibrils *in vitro*, and protects hippocampal neurons from amyloid beta-peptide induced cell death (Niidome, *et al.*, 2007 and Khaengkhan, *et al.*, 2009). The amyloid plaques are formed by the proteolysis of amyloid precursor protein by the by a,  $\beta$  or d secretase enzyme. Therapeutic efforts to target AD have now focused on the disruption of this cascade by blocking these enzymes. Many flavones are identified from *M. ihou* with  $\beta$ -secretase inhibitory activity (Cho, *et al.*, 2011). Cholinesterases are key enzymes that play important roles in cholinergic transmission. Eight flavonoids including kuwanon U, kuwanon E, kuwanon C morusin, morusinol displaying cholinesterase inhibitory (both acetylcholine and butyrylcholine esterase) activity were isolated from the root bark of *M. lhou* L. (Kim, *et al.*, 2011). The neuroprotective effect of oxyresveratrol was studied in *in vitro* model of stretch-induced trauma in co-cultures of neurons and glia, or by exposing cultures to high levels of glutamate. Trauma produced marked neuronal death and oxyresveratrol significantly inhibited this death. Microscopic examination of glia suggested signs of toxicity in cultures treated with 100  $\mu$ M oxyresveratrol, as demonstrated by elevated S-100B protein release and a high proportion of cells with condensed nuclei. Cultures exposed to glutamate for 24 h exhibited ~ 37% neuronal loss, which was not inhibited by oxyresveratrol (Weber, *et al.*, 2012). Studies have demonstrated the beneficial effects of mulberry on the induction of an antioxidant defense system and improvement of memory deterioration in ageing animals (Shih, *et al.*, 2010). The neuroprotective effect of cyanidine- 3-glucoside (C3G) fraction from *M. alba* was studied in oxygen deprivation and glutamate induced cell death in rat primary cortical neurons. C3G did not provide

a protective effect against glutamate induced cell death, but provide protection against oxygen deprived cell death by maintaining the mitochondrial membrane potential (Bhuiyan, *et al.*, 2011) (Fig. 6).

### **The mulberry, *Morus alba* (L.) for skin diseases**

Melanin is a broad term for a group of natural pigments found in most organisms. Melanin is produced by the oxidation of the amino acid tyrosine, followed by polymerization. The melanin pigments are produced in a specialized group of cells known as melanocytes. There are three basic types of melanin: eumelanin, pheomelanin, and neuromelanin. The most common type is eumelanin, of which there are two types—brown eumelanin and black eumelanin. Pheomelanin is a cysteine-derivative that contains polybenzothiazine portions that are largely responsible for the color of red hair, among other pigmentation. Neuromelanin is found in the brain, though its function remains obscure. In the human skin, melanogenesis is initiated by exposure to UV radiation, causing the skin to darken. Melanin is an effective absorbent of light; the pigment is able to dissipate over 99.9% of absorbed UV radiation. Because of this property, melanin is thought to protect skin cells from UVB radiation damage, reducing the risk of cancer, and it is considered that exposure to UV radiation is associated with increased risk of malignant melanoma, a cancer of melanocytes (melanin cells). Studies have shown a lower incidence for skin cancer in individuals with more concentrated melanin, i.e. darker skin tone. However; the relationship between skin pigmentation and photoprotection is still being investigated.

Melanin present in the skin protects from UV induced hyper pigmentation, wrinkling, melasma and cancer. Tyrosinase is an

important enzyme in melanin production and in mammals the skin pigmentation results from the transfer of melanosomes from melanocytes to keratinocytes in the epidermis. *M. alba* L. leaf extract exhibited potent inhibitory effects on mushroom tyrosinase, mammalian tyrosinase, and melanin synthesis in Melan-a cells (Lee, *et al.*, 2002). 2, 4, 2', 4'-Tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone (TMBC), obtained from the stem bark of mulberry, *Morus nigra* (L.) modulated melanogenesis by inhibiting tyrosinase. It inhibited the L-dopa oxidase activity of mushroom tyrosinase which was more potent than kojic acid a well-known tyrosinase inhibitor (Zhang, *et al.*, 2009). Topical applications of mulberroside A, oxyresveratrol, and oxyresveratrol-3-O-glucoside clearly caused depigmentation, reduced melanin indices, inhibited tyrosinase activity, and decreased melanin content in UV induced hyperpigmentation in guinea pig skin. Oxyresveratrol and oxyresveratrol-3-O-glucoside more potently inhibited melanogenesis than mulberroside A. This treatment decreased the expression of MITF gene, that are regulating the transcription of proteins involved in melanocyte pigmentation (Park, *et al.*, 2011). Mulberries also boast a high level of vitamin A and vitamin E, along with a range of carotenoid components like lutein, beta-carotene, zeaxanthin, and alpha-carotene. All of these elements act as antioxidants that specifically affect the skin, tissue, hair, and other areas of the body where free radicals strike. Mulberries can aid in skin care, reduce the appearance of blemishes and age spots, and keep hair shiny and healthy by preventing the oxidative actions of free radicals (Fig. 7).

### **Hepatoprotective potentials of mulberry, *Morus alba* (L.)**

The chemical investigation of the twigs of *M. mesozygia* resulted in the isolation of several

compounds and few of them exhibited hepatoprotective activities (Kapche, *et al.*, 2011). A glycoprotein (MIL) purified from *M. indica* protects against CCl<sub>4</sub> induced liver damage. MIL significantly reduced the activity of alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and thiobarbituric acid-reactive substances (TBARS) in CCl<sub>4</sub> treated mice. It reduced the activity of COX-2 and expression of TNF- $\alpha$  and IL-1 beta in liver from CCl<sub>4</sub>- treated mice. Moreover, supplementation of MIL suppressed stress-activated protein kinase/c-jun N-terminal kinase phosphorylation and activator protein-1 transcriptional activation in livers of CCl<sub>4</sub> treated mice (Oh, *et al.*, 2010). *M. alba* extract significantly reduced the gastric mucosal injury in experimental rats induced by tween 20 and absolute ethanol with marked reduction in the leucocytes infiltration to submucosal layer (Abdulla, *et al.*, 2009) (Fig. 8).

### **The mulberry, *Morus alba* (L.) for gastrointestinal disorders**

The health benefits of mulberries include their ability to improve digestion, lower cholesterol, aid in weight loss, increase circulation, build bone tissues, and boost the immune system. The fruit also helps prevent certain cancers, slow down the aging process, lower blood pressure, protect eyes, and improve the overall metabolism of the body. Mulberries are filled with nutrients that are important for our body, including iron, riboflavin, vitamin C, vitamin K, potassium, phosphorous, and calcium. They also contain a significant amount of dietary fiber and a wide range of organic compounds, including phytonutrients, zeaxanthin, resveratrol, anthocyanins, lutein, and various polyphenolic compounds. Like the majority of fruits and vegetables, mulberries contain dietary fiber, which makes approximately 10% of your daily requirements in a single

serving. Dietary fiber can help to improve digestion by bulking up the stool, thereby speeding up the movement of food through the digestive tract, while also reducing occurrences of constipation, bloating, and cramping. Furthermore, fiber helps to regulate cholesterol levels and can improve heart health when regularly added to the diet. Like the majority of fruits and vegetables, mulberries contain dietary fiber, which makes approximately 10% of your daily requirements in a single serving. Dietary fiber can help to improve digestion by bulking up the stool, thereby speeding up the movement of food through the digestive tract, while also reducing occurrences of constipation, bloating, and cramping. Furthermore, fiber helps to regulate cholesterol levels and can improve heart health when regularly added to the diet.

Exploring and evaluating new and cheap feedstuffs as sources of protein for livestock and other farm animals is an important target for nutritionists to pursue. Competition between man and animal for the same food and the search for alternatives to feed livestock are increasing. The increasing costs of conventional feedstuffs like corn, soybean meal and fish meal for poultry diets is pushing to find less expensive alternatives. One possible feed alternative is tree fodder mulberry leaves (*Morus alba*). Mulberry grows well in the tropics and subtropics, and is reported to have excellent nutritional value. Mulberry leaves are very rich in protein (15-35%), minerals [2.42-4.71% calcium (Ca); 0.23-0.97% phosphorus (P)] and metabolizable energy (1130- 2240 kcal/kg) with absence of or negligible anti-nutritional factors (Omar *et al.*, 1999; Sanchez, 2002; Saddul *et al.*, 2004; Sarita *et al.*, 2006; Wang *et al.*, 2011). The amino acids composition of mulberry leaf meal indicates it is a good source of essential amino acids especially lysine 1.80% and leucine 2.58% (Al-Kirshi *et*



*al.*, 2009). Excellent results have been obtained with mulberry leaves as poultry feed (Chowdary *et al.*, 2009; Al-Kirshi *et al.*, 2010; Olteanu *et al.*, 2010).

### **Antimicrobial effects of mulberry, *Morus alba* (L.)**

The methanolic extract of the bark of *M. mesozygia* as well as its constituents (cycloartocarpesin and different types of moracins) are used for the treatment of infections associated with microorganisms (Kuate, *et al.*, 2009). Prenylated flavonoids isolated from *M. alba* showed antibacterial, antifungal and antiviral activities (Du, *et al.*, 2003 and Sohn *et al.*, 2004). Kuwanon G was isolated from the ethyl acetate fraction of methanol extract of *M. alba* is acting as an antibacterial agent against oral pathogens (Park *et al.*, 2003). Chalcomoracin, a leaf phytoalexin of mulberry tree exhibited considerable antibacterial activity against methicillin-resistant *Staphylococcus aureus* (Fukai *et al.*, 2005). Alisson Macário de Oliveira *et al.*, (2015) evaluated an ethanolic extractives of leaves of mulberry, *Morus alba* (L.) for toxicity to *Artemia salina* (L.), oral toxicity to mice, and antimicrobial activity. Phytochemical analysis revealed the presence

of coumarins, flavonoids, tannins, and triterpenes in the extract, which did not show toxicity to *A. salina* nauplii. No mortality and behavioral alterations were detected for mice treated with the extract (300 and 2000 mg/kg b.w.) for 14 days. However, animals that received the highest dose showed reduced MCV and MCHC as well as increased serum alkaline phosphatase activity. In treatments with the extract at both 300 and 2000 mg/kg, there was a reduction in number of leukocytes, with decrease in percentage of lymphocytes and increase in proportion of segmented cells. Histopathological analysis of organs from mice treated with the extract at 2000 mg/kg revealed turgidity of contorted tubules in kidneys, presence of leukocyte infiltration around the liver centrilobular vein, and high dispersion of the spleen white pulp. The extract showed antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida krusei*, *Candida tropicalis* and *Aspergillus flavus*. In conclusion, the extract contains antimicrobial agents and was not lethal for mice when ingested; however, its use requires caution because it promoted biochemical, hematological, and histopathological alterations.

**Fig.1** Mulberry, the safe therapeutics for human health



Fig.2 Herbal mulberry tea for keeping the diabetes away



Fig.3 The contents of mulberry, *Morus alba* (L.) serve to orchestrate the progression of Healthy heart

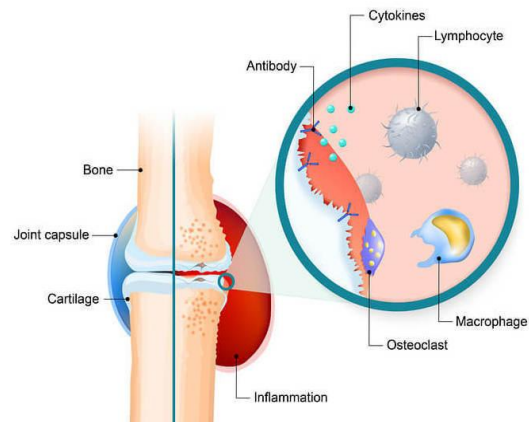


Fig.4 The cancer preventing bioactive compounds from Herbal Sources

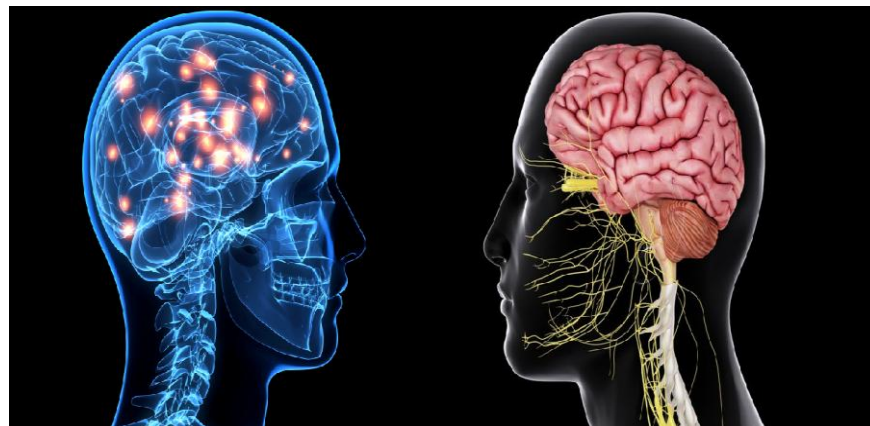
**Bioactive compounds from different sources have shown anti-cancer activity by directly targeting cancer stem cells.**



**Fig.5** The mechanism of inflammation



**Fig.6** The neurological disorders

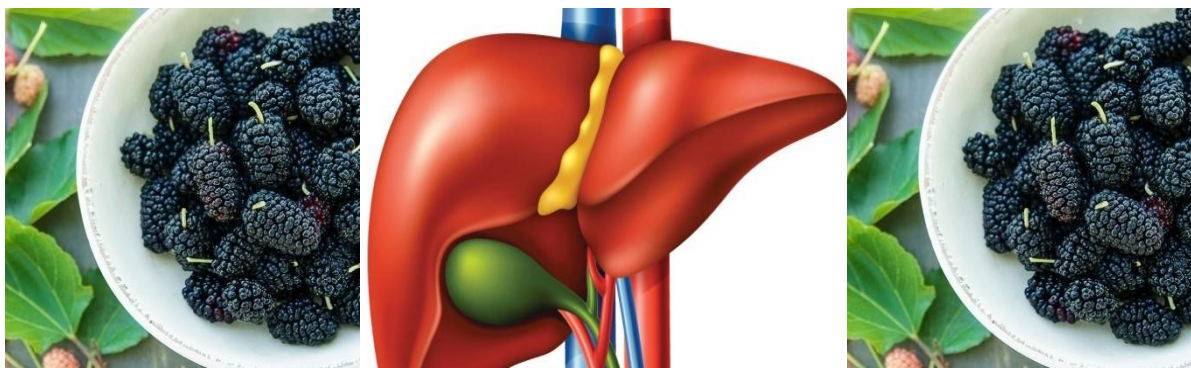


**Fig.7** Mulberry, *Morus alba* (L.) for skin diseases

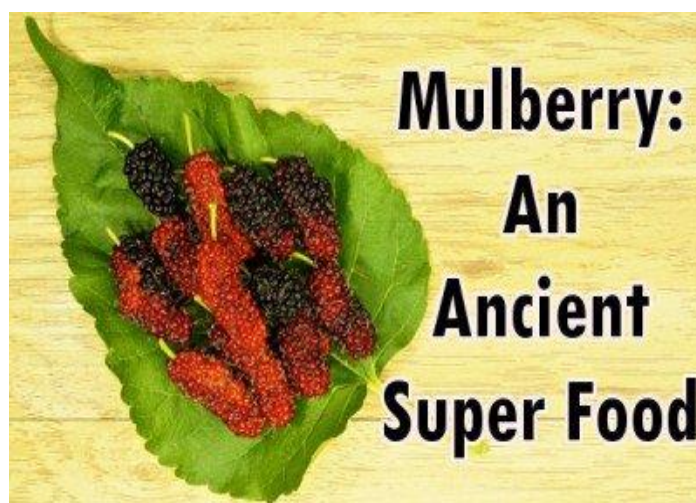




**Fig.8** Mulberry, *Morus alba* (L.) for liver protection



**Fig.9** Mulberry: The ancient super food of silkworms and now, for human being



In conclusion, the mulberry is the one among the most studied plants for pharmacological potential. Research over the years elucidated the existence of a number of active molecules in it. The mechanism included in the exciting pharmacological effect has been studied with a significant number of compounds purified from mulberry. The synthetic analogues of the purified compounds are showed to be effective in the treatment of various diseases. More detailed studies in future with the natural vs. synthetic compounds will clearly show the potential of these compounds in the therapeutic field.

It is expected that in the 21st century more research will be focused on the natural source based compounds to treat various diseases and mulberry is definitely be one of the species to be explored more extensively. One of the carotenoids found in mulberries is zeaxanthin, which has been connected directly to a reduction in oxidative stress on certain ocular cells, including the retinal macula lutea. Furthermore, zeaxanthin functions as an antioxidant and prevents certain damage to the retina, including the free radicals that can cause macular degeneration and cataracts. Vitamin C is a

powerful defensive weapon against any illness or foreign pathogens in the body that antioxidants don't take care of. A single serving of mulberries is almost the entire requirement of vitamin C for the day, but combine that with the minerals and vitamins present in this fruit, and you have a true weapon against illness. Add a few mulberries to your morning meal and watch your immune system soar.

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