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Phytochemistry and Potential Pharmacological Properties of *Morus alba* Plant for Health Benefits: A Comprehensive Review

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***Morus alba* L. is a fast-growing shrub or moderate height tree and considered as Ayurvedic medicinal plant due to its medicinal uses. *M. alba* has high concentrations of phenols, tannins, steroids, flavonoids, alkaloids, terpenoids, and carbohydrates. In this review, approximately 200 papers were reviewed, and finally 96 papers were used to explore the phytochemistry and pharmacological properties of the *Morus alba* plant. The aim of this study is to provide an insightful exploration of biologically active compounds present in the bark, leaves, flowers, and fruits of the *M. alba* plant, and its potential pharmacological effects include anti-inflammatory, antidiabetic, antihyperlipidemic, hepatoprotective, neuroprotective, anthelmintic, anti-obesity, anxiolytic, hypocholesterolemic, antioxidant, antimicrobial, and nephroprotective activity. Phytocompounds present in *M. alba* extracts also have various biological activities, including blood coagulation factors, vasodilation, cytotoxic responses, cytokine storming, sympathetic responses, oxidative stress, cardiovascular, skin, gastrointestinal, skin whitening, and fibrosis, among others. The findings of this review paper showed that different parts of *M. alba* have various pharmacological and therapeutic potential and hence can be used in various herbal formulations as well as health care products.**

Keywords: Antioxidant; Flavonoids; Hepatoprotective; Neuroprotective; Pharmacology; Phytochemistry.

Morus alba (*M. alba*) is known as white mulberry, common mulberry, silkworm mulberry, and in Hindi Tut. *M. alba* is native to Asian countries such as China and India. They are widely cultivated and naturalized everywhere across the world for the process of sericulture as a primary source of food. Furthermore, the leaves are sometimes consumed by humans as vegetables or utilized as cow fodder in many regions. The bark of *M. alba* can be used to make paper, and the fruits are primarily consumed either directly once ripe or are used to make other items, mainly desserts such as jams, jellies, pies, tarts, etc. The various components of the *M. alba* plant (bark, leaves, flowers, and fruits) have enormous potential medicinal properties. Furthermore, they have a lengthy history of use in Traditional Chinese Medicine (TCM) to treat a variety of internal illnesses and infections. It is because they have been found to contain a significant amount of biologically active compounds or constituents

that might have potential use in pharmacological activities that might improve the health of human beings[1,2].

MATERIALS AND METHODS

The phytochemistry and pharmacological properties of *Morus alba* plant were searched online databases by using keywords like "*Morus alba* Plant", "Phytochemistry of *Morus alba", "Taxonomy of Morus alba"*, "Antioxidant properties of *Morus alba",* "Anticancerous effects of *Morus alba",* "Antimicrobial properties of *Morus alba",* "Anti-inflammatory properties of *Morus alba",* "Anti-hyperlipidemic properties of *Morus alba",* "Anti-atherosclerotic properties of *Morus alba",* "Anti-obesity properties of *Morus alba",* "Hypocholesterolemic properties of *Morus alba",* "Anti-diabetic properties of *Morus alba", etc*. in order to explore the pharmacological properties of *Morus alba.*

Plant description

The *M. alba* is a medium-sized shrub or tree, growing 10 to 20 m in height. In young active stems, the leaves can grow up to 30 cm in length with well-rounded elaborate lobes, whereas in older trees, they typically measure 5-15 cm in length with no lobes. Catkins of the single sex are the blooms. Male catkins are 10 to 30 mm long and slender, and female catkins are 2 to 12 mm in length and ovoid. The male flowers do not have sepals and are broadly ovate, whereas the female flowers have suborbicular sepals and are as long as or slightly larger than male flowers.

In the wild plant, the fruit is 1 to 1.5 cm long and deep purple color however in many cultivated plants the fruit color change from white to pink hue (Figure 1).

Taxonomy

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Rosales
Family: Moraceae
Genus: Morus L.
Species: *M. alba* L.

Phytochemical constituents of *M. alba*

M. alba mainly contains phenolic compounds and a balanced content of proteins and minerals. The major bioactive phytochemicals found in *M. alba* are carotenoids, glycosides, saponins, polysaccharides, alkaloids, vitamins, fats (mainly linoleic acid, palmitic acid, and oleic acid), sugars, minerals, and phenolic compounds such as terpenoids, flavonoids (including chalcones and anthocyanins), anthocyanins, and tannins[3]. Other bioactive phytochemicals found in *M. alba* are antibacterial substances, lectins, digestive enzyme inhibitors, stilbene glycosides, coumarins, and unsaturated fatty acids. Leaves of the *M. alba* have the richest source of bioactive substances than the fruits, roots, and stems[4]. The following Table 1 shows the distribution of the various biologically active components obtained from different parts of the plant.

RESULTS AND DISCUSSION

M. alba is a pharmacologically important plant and has various phytochemicals and biologically active phytocompounds. The leaves are rich in flavonoids and have antioxidant, anti-hyperlipidemic, antibacterial, anti-diabetic, skin whitening, anti-obesity, cardioprotective, and cytotoxic properties, whereas the fruits are rich in alkaloids and anthocyanins, which exhibit hepatoprotective properties, anti-obesity, and anti-diabetic (Figure 2). The root and the bark of *M. alba* have anti-inflammatory, antimicrobial, cytotoxic, skin-whitening, and anti-hyperlipidemic properties[22]. The detail pharmacological properties of *M. alba* plant's parts are as follows:

Antioxidant properties

The harmful impacts of xenobiotic compounds on our biological systems are the generation of reactive oxygen species (ROS), causing oxidative damage to several macromolecules. It has been found that natural antioxidants present in mulberry fruit play a significant role in neutralizing ROS and are able

Fig. 1. Fruits and leaves of *Morus alba*

to protect against oxidative stress induced by γ-rays. A reported study suggests that exposure of γ-irradiated in rats causes a significant elevation in the xanthine oxidase activity, malondialdehyde (MDA), and liver enzymes concentrations which can be restored their levels by administration of mulberry fruit powder (MFP)[23].

Oxidative stress is a condition in which the concentration of antioxidants and production of free radicals in the body gets imbalanced. For the neutralization of ROS, the counteraction of the harmful effects is usually done with the help of antioxidants. It has been reported that plant's parts having high phenolic content are known to possess antioxidant properties. Many studies have been performed to investigate the relationship between phenolic contents and antioxidant properties. It has been reported that *M. alba* bark, leaves, flowers, and fruit parts possess antioxidant properties[24]. Bae and Suh[25]reported that the antioxidant activities of *M. alba* ethanol fruit extract vary significantly depending on the plant species used for the experiments. Mature fruits have a high content of anthocyanins, which have strong free radical scavenging activity than vitamin C[26]. In addition to the above studies, another experiment was designed to see the cytoprotective effect of *M. alba* root extract (MARE) on neuroblastoma with the help of flow cytometry along with immunoblot analysis. It was observed that MARE induced down-regulation of protein kinase B (Akt) and FOXO3, a phosphorylation, and an up regulation of caspase-3 activity. In neuroblastoma-B103 cells, it results in the inhibition of growth inductive signals, the generation of ROS, a decrease in the mitochondrial membrane potential, and a fast apoptotic response[27].

Anticancerous effects

M. alba and *M. nigra* leaf extracts and their mixture showed anticancerous effects against mutation induced by radiation in the plant and animal cells. A water-ethanol leaf extract and their mixture composition were administered in a concentration-dependent manner. It was observed that extracts and mixture composition extracts exhibited genoprotective properties. The mutation induced in the animal and plant cells due to the gamma rays and chemical mutagens was successfully inhibited by the extracts and the mixture. The results also demonstrated that they have huge potential to be used as a source of antimutagenicity in food industry products[28].The various components of the *M. alba* tree exhibit cytotoxic effects, or they are found to possess the ability to combat cytotoxic activity. Several experiments have been performed to determine whether the phytochemicals obtained from *M. alba* can exhibit cytotoxic effects on harmful cells or whether they can protect against cytotoxic responses. In a study, flavonoids quercetin-3,7-di-

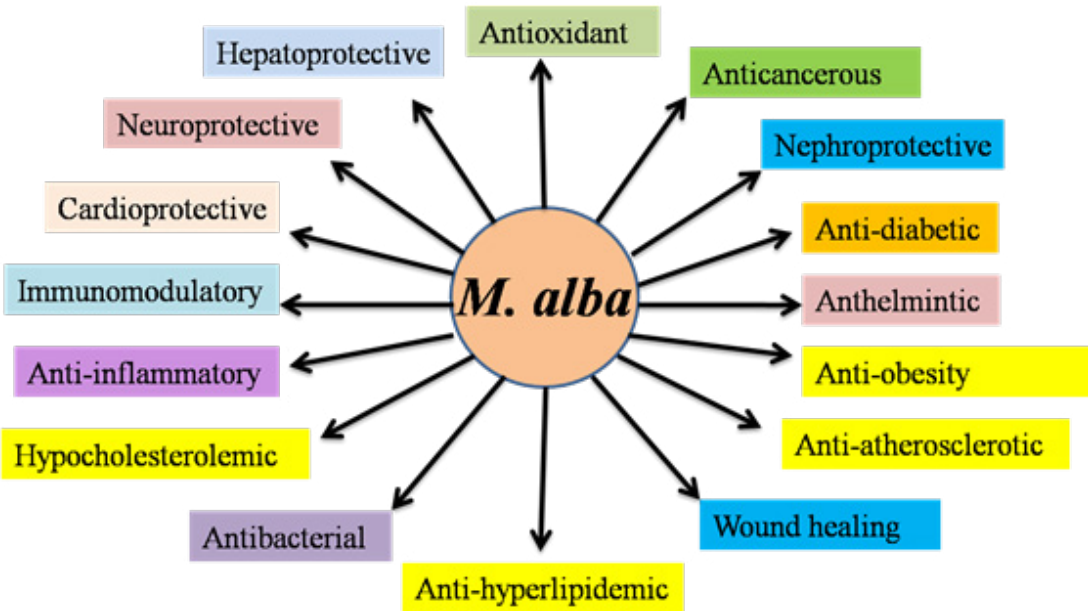

Fig. 2. Pharmacological properties present in different parts of *M. alba* plant

O-β-D-glucopyranoside and quercetin-3-O-β-D-glucopyranoside were extracted from the aqueous methanolic leaf of *M. alba* and reduced the growth of the human promyelocytic leukemia cell line (HL-60)[29,30]. In another study, a flavanone glycoside compound isolated from root bark also showed significant anti-cancerous properties against human ovarian cancer HO-8910 cells[22,31].

Another study was conducted to evaluate the cytotoxic and apoptosis-enhancing activities of albanol A, compound isolated from *M. alba* root bark by using human leukemia cells (HL-60). The finding of this research paper showed that albanol A exhibited strong cytotoxic action and induced early apoptosis. It was postulated that the compound albanol A induced apoptosis in HL-60 cells death by the mechanism of caspase-2 activation and cell death receptor pathway. Hence, albanol A could be a source of drug for effectively treating leukemia[21,22]. The methanolic root and bark extracts of *M. alba* against human colorectal cancer SW480 cells also showed that extracts arrest cell division and induce apoptosis in colorectal cancerous SW480 cells[22,32]. In another study, a mixture of morusinol, isolated from *M. alba* root bark, and doxorubicin, a chemotherapy medication, exerted anti-cancerous properties on the human colon adenocarcinoma cell line (HT-29) by activation of apoptosis and suppression of nuclear factor-kappa B (NF-κB)[33]. Flavonoids morusin, 8-geranyl apigenin, and sanggenon K, isolated from *M. alba* showed anticancerous effects against HeLa cells, MCF-7 cells and Hep-3B cells, respectively [17]. Water and aqueous methanolic extracts also inhibited the growth of human hepatocellular carcinoma HepG2 cells[34]. A study was conducted to understand the basic molecular mechanism for immune system activation and the chemotherapeutic effect of the phytochemicals obtained from *M. alba,* showed increased levels of cytokines, nitric oxide (NO) and tumor necrosis factor-α (TNF-α) and tumoricidal properties of macrophages (Figure 3). Though it was found that phytochemicals never directly triggered on tumor cells, it did display cytotoxicity through activated macrophages. The following flowchart shows the mechanism of how phytochemicals obtained from *M. alba* affect the tumor cells indirectly[35].

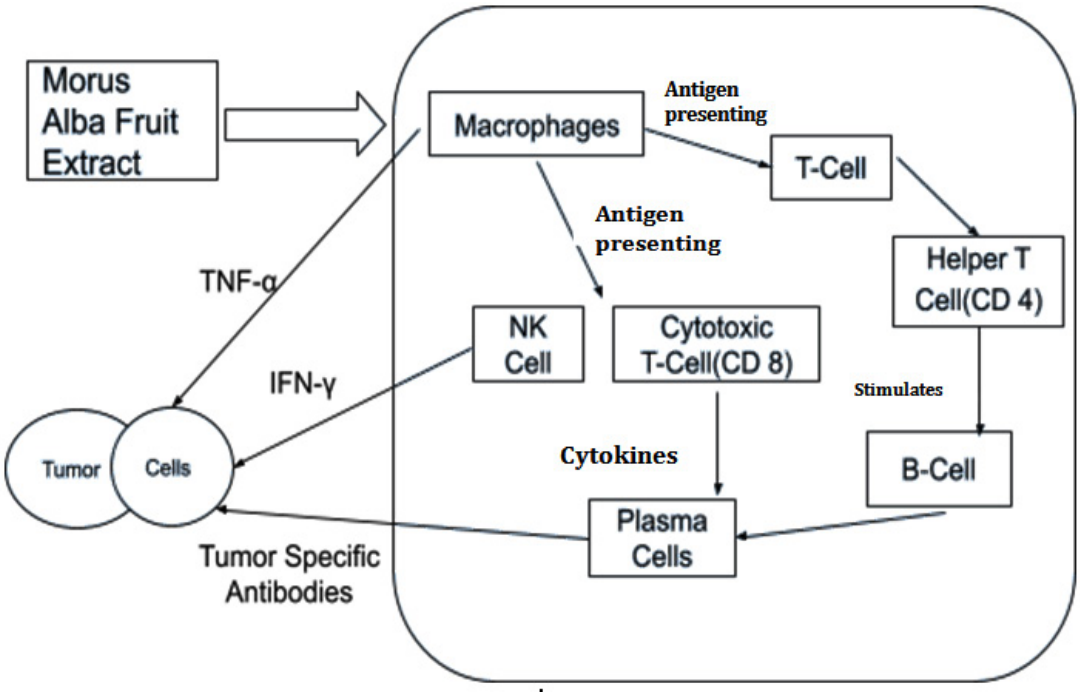

Fig. 3. Summary of the effects of *M. alba* fruit extract against cancer development. TNF-α: tumor necrosis factor alpha; IFN-γ: interferon gamma; NK Cell: natural killer cell; CD: cluster of differentiation; T-Cell: thymus-dependent lymphocyte; B-Cell: B lymphocytes.

Antimicrobial properties

A phytochemical compound, kuwanon G, isolated from *M. alba* methanolic extract showed antimicrobial potential against *Streptococcus sobrinus, Streptococcus sanguis, Porphyromonas gingivalis,* and *Streptococcus mutans*[36]. Mulberrofuran G and albanol B isolated from the root bark strongly inhibit *Staphylococcus aureus, Staphylococcus epidermidis,* and *Salmonella typhimurium*[37]. A study involving chloroform, petroleum ether, and methanolic leaf extracts of *M. alba* was conducted to determine antimicrobial activity against *Candida albicans* and *Aspergillus niger*. It was observed that all the extracts exhibit noticeable antimicrobial activity against these microorganisms depending on the dose[38]. It was found that the flavonoids leachianone G and mulberroside C, which were separated from the root bark of *Morus alba*, have strong antiviral properties against the herpes simplex type 1 virus (HSV-1)[39]. Chalcomoracin, a mulberry tree phytoalexin, was isolated from *M. alba,* has antibacterial properties against methicillin-resistant *S. aureus* (MRSA) bacteria[40].

Anti-inflammatory properties

The different parts of *M. alba* plant showed strong anti-inflammatory properties. Kuwanons C and G, isolated from *M. alba,* activate extracellular signal-regulated kinase (ERK) 1/2 and inhibit NF-κB pathway mediated anti-inflammatory effect[41]. In the same way, oxyresveratrol, which is the active compound obtained from *M. alba* also shows anti-inflammatory activity[42]. Cyclooxygenase 2 (COX-2) gene expression was inhibited by cudraflavone B flavonoid extracted from the roots of *Morus alba*. It blocks the translocation of NF-kB and has properties as a potent inhibitor of tumor necrosis factor-alpha (TNF alpha)[43]. In lipopolysaccharide (LPS)-induced THP-1 cells, a monocyte derived from peripheral blood, resveratrol from *M. alba*

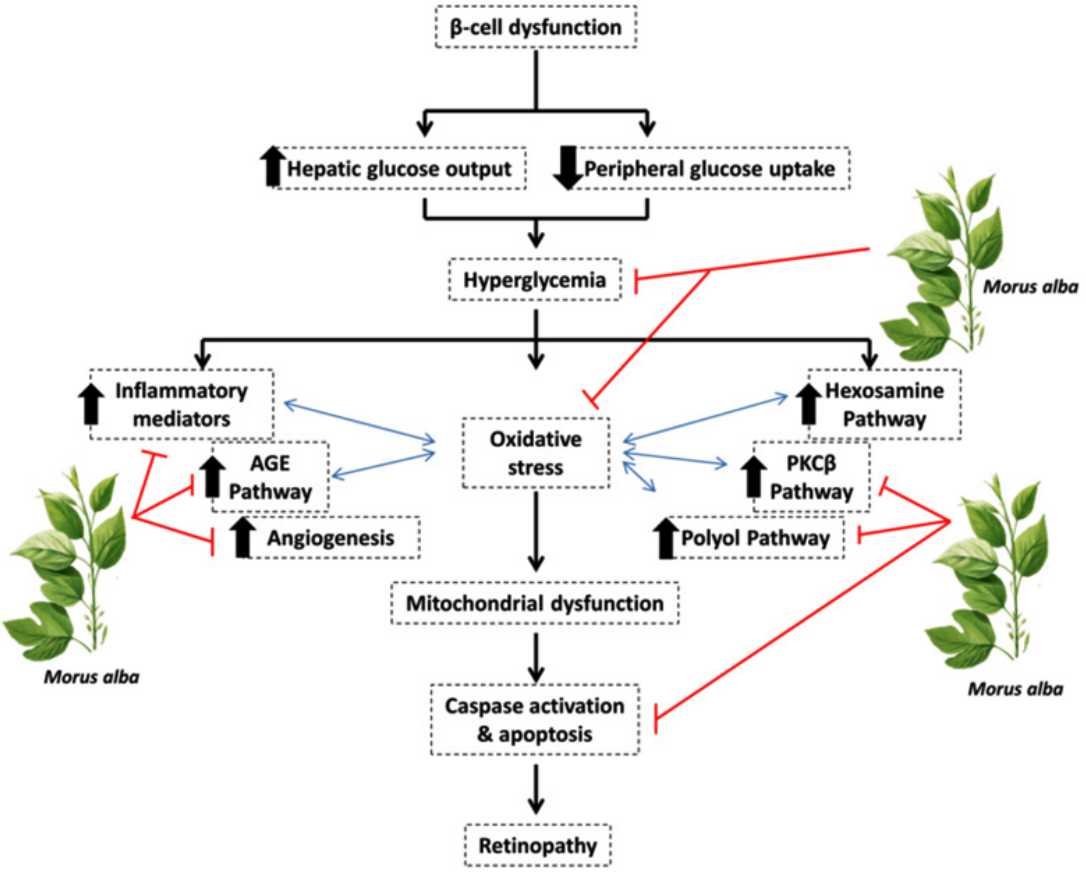

Fig. 4. Protective mechanisms of *M. alba* extract against hyperglycemia-induced retinal damage[63]. AGE Pathway: Advanced glycation end-products pathway; PKC-β: Protein kinase C beta.

Table 1. Distribution of the biologically active components in *M. alba* plant's parts

Parts	Substances	Phytochemicals	References
Bark	Triterpenoids	Moruslanosteryl acetate, moruslupenoic acid A and B,	5
	Phenolic compounds	Maklurein, rutin, isoquercetin, resveratrol, morin, apigenin	6, 7, 8
Fruits	Saturated and unsaturated Fatty acids	Saturated: Palmitic acidUnsaturated: Oleic acid, linoleic acid	8
	Phenolic compounds	Quercetin, chlorogenic acid, kaempferol, rutin, gallic acid, caffeic acid, hydroxybenzoic acid, protocatechuic acid, p-coumaric acid, ferulic acid	8, 9, 10, 11, 12
	Glucosides	Rutinoside cyanine, cyanine glucoside	13
Leaves	Enzyme inhibitors	Moranoline, 1-deoxynojirimycin	14
	Lectins	Hemagglutinin, phytosins, phytohemagglutinin and phytoagglutinin	14, 15
	Saturated and unsaturated Fatty acids	Saturated: Palmitic acidUnsaturated: Oleic acid, linoleic acid, eicosanoids	9
	Phenolic compounds	Kaempferol, quercetin, coumaric acid, apigenin, syringic acid, morin, ferulic acid, luteolin, chlorogenic acid, gallic acid, rutin, caffeic acid, atalantoflavone, umbelliferone, morusin, cyclomorusin	5, 7, 9, 12, 16, 17, 18
Root	Glucosides	Cyanidin 3-O-â-D-glucopyranoside, moran, 1-deoxynojirimycin, glucoside, moracin	19, 20
	Enzyme inhibitors	Oxyresveratrol	12
	Lectins	Albanol	21
	Mulberry flavonoids	Sanggenols, kwanon, mulberrofuran	17
	Phenolic compounds	Resveratrol, luteolin, sinapic acid, gallic acid	7, 9

was found to decrease interleukin-8 (IL-8) release via preventing mitogen-activated protein kinase (MAPK) phosphorylation and activation of NF-κB[44]. Inhibition of phosphodiesterase-4 (PDE4) enzymes causes the accumulation of cAMP and considerably reduces the inflammatory responses. Moracin M obtained from *M. alba* is responsible for the inhibition of PDE-4 enzyme, which is related to anti-inflammatory activity[45]. So that compounds which exhibit such properties can be used as anti-inflammatory agents.

Anti-hyperlipidemic properties

Hyperlipidemia is a condition in which the levels of lipids or lipoproteins get abnormally high and show the most prevalent risk factors for the development of atherosclerosis and cardiovascular disease. Rats that consumed cholesterol were administered extracts from the root bark fractions of *M. alba* in order to test the plant's hypolipidemic and antioxidant properties. The formation of lipid peroxides and inhibition of low density lipoprotein (LDL) atherogenic modifications suggests that the extract obtained from the root bark can exhibit strong anti-hyperlipidemic nature, and it has the potential to act as a hypocholesterolemic nutrient implying that it possesses hypolipidemic properties[46]. In a different investigation, hyperlipidemic rats received an oral aqueous extract from *M. alba* leaves for two weeks showed a reduction in plasma triglycerides levels by 55.01%. In addition to the decrease of the plasma level of triglycerides, hepatic enzymes were also positively restored to the normal level, thus showing the hyper triglyceridemic effects of the leaves of mulberry[47]. The results of both of the above studies were further supported by another study in which phytochemicals mulberroside A and oxyresveratrol isolated from *M. alba* were

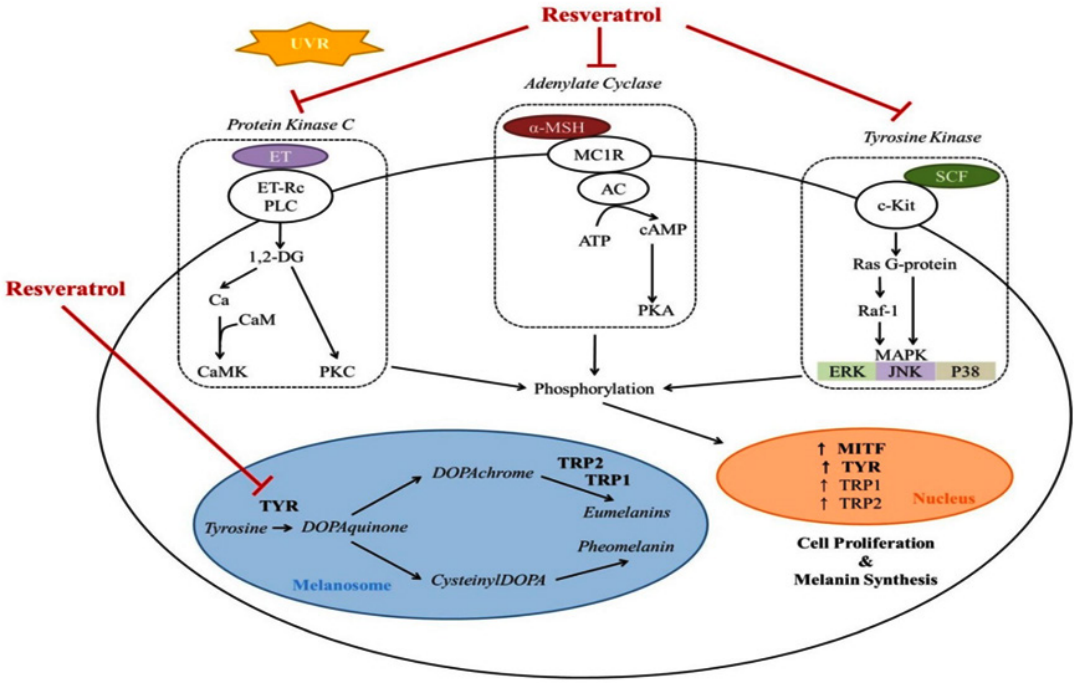

Fig. 5. Effect of resveratrol on melanogenesis and signaling pathways in melanocytes[96]. UVR: Ultraviolet radiation; PLC: Phospholipase C; DG: diacylglycerol; CaM: Calmodulin; CaMK: Calcium/calmodulin-dependent protein kinases; PKC: protein kinase C; á-MSH: a-melanocyte-stimulating hormone; MC1R: melanocortin 1 receptor; AC: adenylyl cyclase; ATP: adenosine triphosphate; cAMP:cyclic-3', 5'-adenosine monophosphate; PKA: protein kinase A; SCF: stem cell factor; Ras G-protein: Ras guanosine-nucleotide-binding protein; Raf: rapidly accelerated fibrosarcoma; MAPK: mitogen-activated protein kinase; ERK: extracellular responsive kinase; JNK: c-Jun N-terminal kinase; TYR: tyrosinase; TRP: tyrosinase-related protein; MITF: microphthalmia-associated transcription factor

examined for anti-hyperlipidemic properties in *in vivo* models which explored that mulberroside A and oxyresveratrol reduce serum lipid levels in hyperlipidemic rats. Results also indicate that oxyresveratrol has strong lipid-lowering potential than mulberroside A[48].

Anti-atherosclerotic properties

It has been reported in many studies that the fruits and leaf extracts of *M. alba* are known to exhibit anti-atherosclerotic effects in rodents. An experiment involved the administration of 1% mulberry leaf powder as a dietary supplement to see the effects on atherogenesis in apolipoprotein-E deficient mice. After 12 weeks of therapy, there was a noticeable increase in the mulberry leaf group's lipoprotein oxidation lag time when compared to the control group. Furthermore, a 40% decrease in the size of the aortic atherosclerotic lesion was seen in the mulberry leaf group. This could be attributed to the presence of antioxidant substances that have potent inhibitors of lipoprotein oxidation and free radical scavenging[49].

An experiment was conducted in which New Zealand white rats were administered with *M. alba* water extract (MWE) in addition to a high cholesterol diet (HCD) to determine the hypolipidemic and anti-atherosclerotic properties of *M.alba*. It was observed that the levels of low-density lipoprotein cholesterol (LDL-C), cholesterol and triglyceride were lower in the serum of rabbits administered with MWE than control group. By including the extract in the rabbits' diets, the amount of atherosclerosis in the aorta was significantly reduced. There was a reduction in the aortic atherosclerotic lesion in the blood vessels of rabbits as observed in the histopathological examination. In addition to the inhibition of LDL-oxidation, previously existing data and findings from the experiment suggest that the extract directly affects the antihyperlipidemic effect in animals. Administration of freezer-dried mulberry fruit powder (5% to 10%) to rats on a high-fat diet lowered the triglyceride content, total cholesterol, increased the levels of antioxidant enzyme and inhibited malondialdehyde (MDA), a product of lipid peroxidation. This suppressed the growth of atherosclerosis in the rats[50].

Anti-obesity properties

In diet-induced obese mice, the effects of *M. alba* ethanol leaf extract on obesity were investigated. It was found that the extract had a strong anti-obesity impact and reduced body weight and adiposity. Additionally, it controlled the mice's hepatic lipid accumulation. It has been suggested that receptor antagonism may be the cause of the extract's anti-obesity effects[51]. Aqueous mulberry leaf extract was given to male hamsters on a high-fat diet as part of a study. This led to a significant a reduction in body weight, reduction in the cholesterol, serum triacylglycerol, and free fatty acid concentrations, and in addition to that the HDL/LDL ratios were elevated[52]. There was another recent study conducted in which obese mice were administered with a combined mixture of the leaf and fruit extract of *M. alba* for 12 weeks. This was because the combination mixture reduced the oxidative stress and, in addition to that, ameliorated the cholesterol transfer proteins[53].

Hypocholesterolemic properties

Rats that were fed cholesterol were given methanolic extracts from the root bark fractions as part of an experiment. Three distinct *M. alba* fractions (MRBF-1, MRBF-2, and MRBF-3 fractions) were given orally to the hypercholesterolemic rats for a period of 15 days in order to monitor any hypocholesterolemic effects. The findings indicated that taking MRBF-2 and, to a limited extent, MRBF-3 portions of *M. alba* root bark possesses potential tendency to act as a powerful antioxidant and a hypocholesterolemic activity by the formation of lipid peroxides and inhibition of LDL atherogenic modifications in hypercholesterolemic rats[46]. In another experiment, analysis of various bioactive components of Polish *M.alba*, especially the ethanol-water extract obtained from the leaves, showed hypocholesterolemic properties. It was mainly conducted to examine the effect of the extract on plasma antioxidant capacity and plasma lipids in rats that have been fed a high-fat diet for 6 weeks. Additionally, the extract was also added as a supplement to the diet of hyperlipidemic wistar rats. It was observed that both the antioxidant activity and LDL cholesterol levels were found to have significantly decreased. It was postulated that aqueous ethanolic extract from the leaves of *M. alba* was an excellent source as a supplement to the diets for hypercholesterolemic individuals[54]. The phytochemicals present in *M. alba* have been known to contain various

biologically active compounds that could prevent atherosclerosis development caused by high cholesterol consumption. It was postulated that *M. alba* leaves prevented abnormal blood vessel reactivity caused by hypercholesterolemia[55].

Anti-diabetic properties

An investigation was carried out on streptozotocin-induced diabetic rats to examine the effects of mulberry leaf ethanolic extract by measuring blood glucose, oxidative damage, and glycation levels. The experiment involved the daily administration of 1g/kg *M. alba* for six weeks. From this experiment, it has been found that both 4U/kg insulin and 1g/kg*M. alba* extract decrease blood glucose level in the same extent. Results suggest that long-term *M. alba* treatment has antihyperglycemic, antiglycemia, and antioxidant benefits in chronic diabetic rats. Thus, they can be considered a beneficial food supplement for people suffering from diabetes[56]. An additional investigation exploring the potential anti-diabetic effects of *M. alba* fruits and leaves in rat models revealed that the leaf extract significantly reduces postprandial glucose levels by blocking the transit of glucose and á-glucosidase[57]. Mulberry root bark extract was given to diabetic rats that had been induced with streptozotocin (STZ) for ten days. The results of this investigation indicate that serum glucose and lipid peroxides were significantly reduced, and that this was followed by an increase in insulin levels[58]. Research has also shown that the pancreas of diabetic rats benefited from the use of *M. alba* leaf extract. Different doses of mulberry leaf extract were given to diabetic rats for 35 days[59]. The findings suggested that this plant's extract could lower blood sugar levels by regenerating â cells, restoring normal islet diameter, and balancing the pancreatic weight.

In a study, the alpha-glucosidase inhibitory components obtained from mulberry tea were studied. There is a significant observable difference in the inhibitory activity of different tea products against both sucrase and maltase. It was observed that during the preparation of the tea, if they were allowed to be brewed for 3-5 minutes, they proved to be the most effective in the inhibition of enzymes. On a Caco-2 cell culture experiment, the amount of glucose on the apical and basal sides of the cell monolayers decreased. It was shown that plant extracts can be consumed as an antidiabetic herb tea and have an inhibitory impact on the enzymes maltase, sucrase, and alpha-glucosidases[60]. According to a study by Hunyadi[61], type II diabetic rats' blood glucose levels decreased after taking an 11-day dose of *M. alba* leaf extract in aqueous ethanol. They postulated that the extract's anti-diabetic properties took place in the presence of rutin and chlorogenic acid. When Zucker diabetic fatty rats were given mulberry fruit extract, their blood glucose levels were found to be much lower than those of the control group. At the maximum dosage, there was no observable decline in the insulin levels, and no discernible changes were observed in the histology of the pancreatic β-cells[62]. An investigation was carried out to ascertain the cellular mechanisms by which white mulberry mitigates diabetic retinopathy (Figure 4). The mechanism examined the preventive impact of *M. alba* leaf ethanolic extract on angiogenesis, oxidative stress, inflammation, and apoptosis in diabetic retinopathy. *M. alba* extract (100 mg/kg) was given daily to diabetic rats triggered by streptozotocin (STZ) for duration of 16 weeks. The findings suggest that *M. alba* may be susceptible to developing diabetic retinopathy[63].

Effect on cardiovascular diseases

According to Lee[64], morusinol obtained from *M. alba's* root bark prevents the production of thromboxane B2 (TXB2) in cultured platelets. It also inhibited the induced platelet aggregation. Because of its antiplatelet action, it is highly efficient in vivo in preventing arterial thrombosis. It also has beneficial effects on stroke through platelet activation modulation. Chan[65] explored that the leaf extract of *M. alba* inhibits the migration of the vascular smooth muscle cell (VSMC). It was found that phosphorylation of focal adhesion kinase (FAK) and Akt, suppression of NF-kB, guanosine triphosphatase expression, and reduction of MMP-2, MMP-9, and metalloproteinases (MMPs) activities, increase vascular smooth muscle cell (VSMC) migration. A study was conducted to examine the effects of *M. alba* leaf extracts on aortic VSMC in rabbits fed a high-cholesterol diet. It was found that the mulberry leaf polyphenol extract inhibits VSMC proliferation and migration, and in addition to that, they also reduce the atheroma burden in the vascular wall[66].

Cardioprotective effects

To investigate the cardioprotective

effect of mulberry leaf powder in autoimmune myocarditis rats, and results suggested that a diet having mulberry as a supplement has the potential to preserve cardiac functions in experimental autoimmune myocarditis[67]. The mechanism by which cardiac functions were retained against oxidative stress due to activation of MAPK pathways. This also enables protection against endoplasmic reticulum stress-mediated apoptosis. There is a significant reduction in the mast cell density, cardiac fibrosis, myocyte apoptosis, and myocardial levels of Sarco/endoplasmic reticulum Ca^{2+} ATPase2, caspase12 cellular infiltration, and phosphor p38 mitogen-activated protein kinase with supplementation of mulberry leaf. An experiment was conducted *in vivo* using male wistar rats to assess the cardioprotective effect of the extract obtained from the leaves of *M. alba* against isoprenaline-induced myocardial infarction. The findings of this study indicate that the leaf extract of *M. alba* exhibits a cardioprotective effect by increasing antioxidant defense system and lowering lipid peroxidation during isoprenaline-induced myocardial infarction in rats[68].

Neuroprotective effects

The accumulation of â-peptides leads to the formation of plaque in individuals suffering from Alzheimer's disease. Kaempferol-3-O-glucoside, and kaempferol-3-O-(6-malonyl) glucoside obtained from the methanolic extract of *M. alba* inhibit the formation of amyloid beta-peptide (1-42) fibril. They also protected the hippocampal neurons against amyloid beta-peptide (1-42)-induced neurotoxicity. The results indicated that there may be hope for treating Alzheimer's disease with methanolic extract derived from *M. alba* leaves; nevertheless, additional research is needed to confirm the extract's effectiveness.[69,70].

In an experiment, the neuroprotective effects of oxyresveratrol were tested on two different pathologies. One is an *in vitro* model of co-cultures of glia and neurons with stretch-induced trauma, and the other is by exposing the culture to high levels of glutamate. The cultures were treated with different concentrations of oxyresveratrol obtained from *M. alba*. It was observed that oxyresveratrol significantly inhibited the neuronal death caused by trauma. But in the case of the culture exposed to glutamate, it was not successful in inhibiting the neuronal loss caused by extreme exposure. It was concluded that additional experiments to study the effect of oxyresveratrol in cases of traumatic injuries have to be conducted[71]. The effect of *M. alba* on glutamate and oxygen-glucose deprivation-induced cell death in cortical neurons of rats was observed.Cyanidin-3-glucoside (C3G) compound from the fruit of *M. alba* given to the rats and found that the extract was able to preserve the mitochondrial function of the neurons and prevented the damage of the membrane in primary cortical neurons exposed to oxygen-glucose deprivation. But C3G didn't provide any sort of protection in case of glutamate-induced cell death[72].

Hepatoprotective effects

An investigation was carried out to ascertain the protective mechanism of mulberry water extracts (MWE) in CCl_4-induced hepatic wistar rats. The extract was administered orally, and it led to a reduction of lipid peroxidation and inhibition of liver fibrosis and lipid deposition. The findings of this experiment indicatethat the mulberry extract has hepatoprotective effects against fibrosis by inhibiting the proinflammatory gene expression and decreasing the lipid peroxidation[73]. Rats were used in another experiment to test the hepatoprotective effects of water, petroleum ether, alcohol-based *M. alba* extracts, and chloroform against paracetamol-induced hepatotoxicity. From this experiment, it was observed that CCl_4 present in the paracetamol led to an increase in the levels of alanine phosphatase (ALP), serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), serum bilirubin, and caused significant damage to hepatocytes. According to the findings, pre-treating the rats with *M. alba* leaf water and alcoholic extracts minimized the hepatotoxicity caused by paracetamol [74]. It was postulated that the hepatoprotective properties of the alcohol-based extract occurred by the presence of carbohydrates, alkaloids, tannins, flavonoids, and steroids, whereas the water extract possessed flavonoids, carbohydrates, and alkaloids. To test *M. alba* hydroalcoholic extract's hepatoprotective properties in mice with CCl_4-induced hepatic liver damage, the findings of the experiment indicate that hydroalcoholic extract of *M. alba* leaves significantly reduced the levels of alanine aminotransferase (ALT) and aspartate

aminotransferase (AST) compared to the CCl_4 group[75].

Antihelmintic properties

An experiment was conducted to determine the anthelmintic capacity by subjecting Indian earthworms to different concentrations of *M. alba*petroleum ether, chloroform, and methanolic leaf extract. The anthelmintic capacity was obtained by determining the time taken for paralysis and death of the earthworms. The anthelmintic capacity of the extracts at different dosages is quite comparable to that of the effect produced by albendazole, which is the standard antihelmintic drug. The study concluded that *M. alba* contains steroids, triterpenoids, tannins, flavonoids, and alkaloids, hence having anantihelmintic effect[38]. The antihelmintic activity was further demonstrated by the examination of alcohol, petroleum ether *M. alba* leaf aqueous extract. The time taken for paralysis and the death of the worms at different concentrations of plant's extract was used to determine the anthelmintic capacity. The results proved that petroleum ether, alcohol, and aqueous extract of *M. alba* leaf caused paralysis of the worms and at higher doses even led to their death[76].

Research was done to determine the anthelmintic potential of water extract prepared from the leaves of *Azadirachta indica, Dalbergia sisso*, and *M. alba* against the ova and adult worms of *Haemonchus contortus*. Three different types of tests *i.e.* egg hatch test, the egg count reduction test and the adult motility assay were carried out to determine the anthelmintic capacity of the plants. The findings of this study suggest that the extract obtained from the leaves of the mentioned plants possesses antihelmintic properties as they can induce anti-parasitic activity in the test subject[77]. In an experiment, *Pheretima posthuma*, an Indian earthworm, was subjected to aqueous, ethanolic and hydro-alcoholic extracts prepared from *M. alba* bark. The extracts were administered to the earthworms in a dose-dependent manner, and the time taken for paralysis and death of the earthworms was recorded. Normal saline was used as the control group and piperazine hydrate as a reference standard. The anthelmintic capacity of the extracts depended on the dosage administered to the earthworms. The results suggested that all the extracts possess anthelmintic properties. It was also found that the hydro-alcoholic extract is more potent than the other extracts, but additional experiments need to be conducted to validate the efficacy and usage of *M. alba* as an anthelmintic drug[78].

Nephroprotective activity

The protective effect of hydroalcoholic extract and flavonoid fraction from leaves of *M. alba* was evaluated against cisplatin-induced nephrotoxicity in male rats. It was observed that the hydroalcoholic extract did not affect the increased serum levels of blood urea nitrogen (BUN) and creatinine (Cr) due to cisplatin, but on the other hand, the flavonoid fraction significantly decrease the serum concentration levels of Cr and BUN however, no significant effect was observed on serum nitric oxide levels. The findings suggested that the flavonoid fraction obtained from the leaves of *M. alba* can be used as a nephroprotective agent against the cisplatin-induced nephrotoxicity[79]. In another experiment, the hydroalcoholic extract from *M. alba* on the isoniazid-induced nephrotoxicity in albino rabbits, a drug used for the treatment of tuberculosis, explore that the hydroalcoholic extract had a significant nephroprotective effects against isoniazid induced nephrotoxicity in the rabbits. Histopathological analysis and the HPLC analysis were also conducted, which indicate that isoniazid showed significant decrease in the serum of rabbits that were treated with the hydroalcoholic extract of *M.alba*. Thus, it was suggested that hydroalcoholic extract obtained from *M. alba* reduced the nephrotoxicity induced by isoniazid and can potentially be used as an alternate drug[80]. Ullah[81]reported the nephroprotective effects of ethanolic extract of *M. alba* in rabbits in which rabbits were administered with the ethanolic extract along with gentamicin for three weeks. The findings indicate that the plant extract inhibited the level of Cr, BUN and uric acid. Histopathological analysis also indicated that the extracts possess a protective capacity.

Immunomodulatory properties

Immunoglobulins (Ig), also known as antibodies, are a 'Y'- shaped protein molecule that is mainly produced by plasma cells. They are present in the blood, exocrine fluid, and tissue fluid. Amongst all of them, the body's humoral immunity, which consists of IgG, IgA, and IgM in the serum of almost all mammals[82]. The immunomodulatory

effect was tested by administering oral doses of methanolic extract of *M. alba* both at high and low concentrations along with *Ocimum sanctum* as a standard drug. It was observed that in both cases, the levels of immunoglobulins in serum were high. It has been observed that an increase in antibody levels in the blood circulation, an increase in the phagocytic index, and increase in the adhesion of neutrophils led them to postulate that *M. alba* increases both the cellular immunity as well as humoral immunity[83]. In addition to that, an experimental study was carried out on weanling pigs by adding mulberry (*M. alba*) leaves in their dietary supplements to test the effect on the immune parameters of the pigs. The increase in the levels of immunoglobulin G (IgG) and immunoglobulin M (IgM) in the pigs indicated that an increase in the formation of antibodies. Such a rise in antibody and cytokine levels in the blood might indicate that the cellular and humoral immunity has improved in the test animals'[84]. To study the mechanisms of the immune response, a xenograft mouse was exposed to *M. alba* fruit extract (MFE). An improved chemotherapeutic activity was obtained with a significant increase in the IgG levels[35].

Effect on blood coagulation

Blood coagulation is the process by which the blood converts itself from liquid to gel form, thus leading to the formation of a blood clot[85]. Thrombosis is a process in which blood clotting takes place within a blood vessel, known as a thrombus. It prevents blood flow within the blood vessels. Thrombosis is caused by activation of platelet aggregation, adhesion, and induction of extrinsic and intrinsic blood clotting systems, which cause fibrin formation. So to prevent thrombosis, it is necessary to inhibit platelet function. The antiplatelet activity of *M. alba* leaf extract (MAE) was studied using rat platelets *i.e* an investigation/experiment was conducted to determine whether *M. alba* leaf extract affects platelet aggregation or not. An arteriovenous shunt model of a rat was used to assess the formation of thrombus *in-vivo*. The following flowchart shows the mechanism of the inhibitory effect of MAE.

The results obtained from the *in-vitro* experiment showed that the ethanol extract of *M. alba* leaf (MAE) has antiplatelet and antithrombotic properties because it inhibited the suppression of platelet aggregation induced by collagen and reduced the thrombus formation[86]. Another experiment was carried out by using an *in vitro* rabbit platelet aggregation to determine the antiplatelet potential of flavonoids morusinol from plant bark root against ferric chloride induced thrombosis model. The results of this experiment signify that morusinol significantly suppresses platelet aggregation in a concentration-dependent manner. In addition to that, it was observed that phytocompounds can significantly inhibit arterial thrombosis formation[87].

Effect on vasodilation

Vasodilation means the widening of blood vessels, which usually occurs at the surface of the skin and it causes an increase in the blood flow and provides a feeling of warmth[88]. The vasodilatory action of ethanolic extracts from *M. alba* leaves was investigated on rats and rabbits. Result showed that mulberry leaf extract showed dose dependent increase in the nitric oxide levels. When the rats were treated with the lowest dosage of ethanolic mulberry leaf extract, at minute 30, there was a marginally significant ($P<0.05$) difference in the NO level as compared to the negative control. The highest concentration of NO in the serum was detected at 202.67 mg/kg BW of mulberry extract. As a result, this dosage was selected for the rabbit ear vasodilatation test. At minute 60 following extract administration, it was found that the mulberry leaf ethanolic extract could considerably widen the rabbit ears' large and small capillaries in comparison to the negative control ($P<0.05$). Thus, it can be claimed that mulberry leaf ethanolic extract has a vasodilator effect, most likely as a result of raising serum NO levels[89].

Effect on cytokine

In a cytokine storm, it has to produce more and more cytokines, even if this is insufficient to destroy the virus, and this cycle continues indefinitely. Now, because of this, the suppressor cells don't receive the messages to turn off the production. This potentially fatal systemic inflammatory syndrome is known as "cytokine storm" and caused a variety of infections, malignancies, autoimmune diseases, and monogenic disorders. They are characterized by high amounts of circulating cytokines and immune cell hyperactivation[90]. So, there will be a barrage of immune cells going to those places, thereby

damaging any vulnerable organ. Research was carried out to evaluate the impact of kuwanon-G isolated from the root barks of *M. alba* to study the influence phytochemicals on the cytokine storm. In the asthmatic mice model, Kuwanon G compound reduces the levels of IgE, IL-4, IL-5, and IL-13 cytokines in the bronchoalveolar lavage (BAL) fluids, which indicates that Kuwanon G has properties to inhibit the development of asthma by reducing the cytokines production[91].

Effect on sympathetic responses

A rat model of chronic stress (CS) was used in the study to assess the adaptogenic properties of the ethyl acetate soluble fraction of the methanol extract of *M. alba* roots. Chronic stress was shown to cause severe mental depression, cognitive impairment, elevated stomach ulcers, elevated blood cortisol levels, and hyperglycemia. The CS-induced problems were significantly reduced when the ethyl acetate soluble fraction of the methanol extract of *M. alba* roots was administered[92]. Thus the findings suggest that the administration of *M. alba* has the potential of reducing the stress thereby, in turn, reducing the sympathetic responses.

Effect on fibrosis

Fibrosis is characterized by the unregulated development of extracellular matrix components in place of normal tissue, which results in significant tissue remodeling and the development of permanent scar tissue[93]. A study was conducted to ascertain whether or not administering *M. alba* leaves to mice on a high-fat diet may mitigate the effects of obesity-induced hepatic lipogenesis, oxidative stress, and fibrosis. It was observed that *M. alba* leaf extract treatment significantly reduced lipid biosynthesis and hepatic fibrosis markers. Therefore, supplementing with *M. alba* leaf extract may be a promising therapeutic agent for obesity-related fatty liver disease by controlling the synthesis of fibrosis, hepatic lipid metabolism, and the antioxidant defense system[94]. The effect of *M. alba* on other types of fibrosis is still yet to be discovered, and more studies have to be made to determine whether the phytochemicals present in the biologically active components of *M. alba* would have any effect or not.

Skin whitening effects

Melanin is a natural skin pigment, and the amount of melanin in an individual decides the color of hair, skin, and eyes. Melanin is produced by melanocytes, and the process of creation is known as melanogenesis. Tyrosine, an amino acid, undergoes oxidation in this complex chemical process, which is followed by polymerization. Melanin protects the cells of the skin from harmful UV radiation, thereby protecting the skin from melasma, skin cancer, hyper pigmentation, and wrinkling. Mulberroside F, which was derived from the methanolic extract of *M. alba* leaves, was found to have inhibitory effects on tyrosinase activity and the formation of melanin by melanocytes in a study. It was also able to protect against auto-oxidation. The findings suggested that mulberroside F obtained from the leaves of *M. alba* can potentially be used as a skin protective agent[19]. A study involved the topical application of oxyresveratrol, mulberroside A and oxyresveratrol-3-O-glucoside to brown-skinned guinea pigs to study the potential inhibitory effect on the harmful UV radiation. It was observed that all three of them successfully inhibited tyrosinase activity; significantly reduced the melanin content in the skin of guinea pigs exposed to the harmful UV rays and also caused depigmentation. Out of the three, oxyresveratrol was found to exhibit the highest anti-melanogenesis effect and mulberroside A, the lowest. It was suggested that the compounds extracted from *M. alba* have the potential to be used as a skin whitening agent as they successfully reduced the pigmentation (Figure 5)[95].

CONCLUSIONS

The various bioactive compounds present in the extracts isolated from the different parts of *M. alba* plant have potential pharmacological activities, which include antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, antidiabetic, anti-atherosclerotic, neuroprotective, anthelmintic, anxiolytic, hypocholesterolemic, anti-obesity, antimutagenic, and nephroprotective properties, and also have a positive impact on various parameters such as immunoglobulin levels, blood coagulation factors, vasodilation, cytotoxic responses, cytokine storming, sympathetic responses, oxidative stress, and fibrosis. Although the different extracts and isolated compounds from *M. alba* plant have many therapeutic implications, but further research need to be conducted for

the exploration of antiviral activities of *M. alba* especially for SARS-CoV, Ebola, MERS-CoV, H1N1 pandemic, measles virus, and Nipah virus diseases. The conclusions of review paper suggest that the various *M. alba* plant parts' extracts have significant pharmacological properties and can be used as potential source for the preparation of various health care products and herbal formulation to treat various diseases.

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Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials

Authors' Contribution

Pankaj Singh and Mamta Shukla: Conceptualization, writing, reviewing, and supervision; Anuja Mishra, Rajeev Natesh Kumar: Writing, review and editing; Swaroop Kumar Pandey: Analysis, review and editing.

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