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NOVEL PHARMACOLOGICAL ACTIVITIES AND AGENTS OF *MORUSALBA*

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ABSTRACT

M. alba belongs to *Moraceae* family commonly known as mulberry in Pakistan locally known as Shahtoot, had very old medicinal background. In old Chinese medicine mulberry has been used for treatment of number of diseases including cancer, in inflammation and for treatment of viral infections. *M. alba*is a reach plant contains many useful chemical constituents as flavonoids, glycosides, flavones, Flavonols, alkaloids and many other pharmacological compounds. These Compounds are used for treatment of many bacterial and viral disease. This study mainly emphasis the number of chemicals can be isolated from mulberry and possible pharmacological uses of active constituents of *M. alba* including antiulcer, anti-cancer, antifungal, antibacterial, skin caring, hepatoprotective, Cardioprotective and other medicinal uses of *M. alba.*

Keywords: Pharmacological, Alkaloids, Phytochemicals, Flavonoids, Glycosides and *M. alba*.

INTRODUCTION

Less toxic approaches for treatment of diseases always been preferred by human that's why use of compounds present in nature got much attention since late 19s rather than synthetic ones, as phytochemicals compounds with least toxicity and are much effective for number of diseases[1, 6]. For such purpose *Moraceae* family is very popular one of specie *Morus alba* is mulberry 10-20m tall small to medium, fast growing short lived tree, mostly found in China commonly used to feed silkworm also native to subtropical region of Asia, Europe, America and Africa had number of pharmacological uses[2,5]. Mulberry is from genus *Morus* with 24 species and one sub specie and known 100 varieties[19]. Leaves of white mulberry are glossy green coordinated at base, 5.0-7.5 cm varying size petioles, Many flowers form drupes around fruits form a sorosis, on ripening fruit color turn white from green (white mulberry) are one of main characteristics of *Morus alba*[7]. Since thousands years various parts like, bark, stem, leaves root of *M. alba* beingused as anti-bacterial, inflammatory and hypoglycemic agent even the evidences for treatment of hypertension, cold and fever in old chines traditions are important to see[3]. *M. alba* is a natural food additive to contains number of constituents like fibers, vitamins, proteins, lipids, sugar, carbohydrates and minerals[4, 15]. Various chemical active constituents like polysaccharides, flavonoids and alkaloids, triterpenes, amino acid, Iminosugar, 1-deoxynojirimycin(DNJ) & 2-O-α D-galactopyranosyl- DNJ (GAL-DNJ), fagomine and also contains quercetin, isoquercitrin, rutin and quercetin 3-(6-malonylglucoside). In pharmaceutical industries the use of flavonoids is very important[8, 10]. From the stem barks of Mulberry many constituents been reported like albanol A and B, mulberranol, cyclomulberrochromene, mulberrochomene, cyclomulberrin, mulberrin, lupeol, α-amyrin, β-amyrin, lanost-7-en-3-on, β-sitosterol and phytol. Many of these has inhibitory effects as α-amyrin, β-amyrin and lupeol show inhibitory effect in rat liver cells for kinase protein and

also are anti-inflammatory while β-Sitosterol play very important role in biosynthesis of steroid and also on 5-α-reductase had strong inhibitory effect[9,13]. Mulberry has lots of medicinal uses as antidiabetic, expectorant, diuretic, antiphlogistic, using leaves in powdered can lower the triacylglyceride, blood and urine glucose, LDL-cholesterol and VLDL-cholesterol and fatty acid in type-2 diabetes patients when used by oral rout of administration, for antidiabetic effect the agents glycoproteins and piperridine alkaloid been extracted from roots of *M. alba*[10].

Pharmacological Activities and Medicinal Use of *M. alba*

Regarding the natural drugs plants are major and a huge source used and been used against many diseases and many organisms that shows the tremendous pharmacological activities of plants against certain organism and diseases. Mulberry had enormous number of medicinal uses reported so for with the time. Pharmacological activities are discussed and phyto-chemicals are shown in the table-1.

1. Antiulcer activities of M. alba

This study carried out for newly extracted compounds from Mulberry using spectroscopic technique know a column chromatography. These extracted compounds identified using different techniques like IR, UV, ^{1}H Nuclear Magnetic Resonance, ^{13}C Nuclear Magnetic Resonance and mass spectroscopy. These compounds tested for antiulcer activity in the pylorus-ligation- and ethanol-induced ulcer models. Then SOD, CAT, GR, GPx, GSH and LPO levels were calculated biochemically. Five compound extracted one of these compound that is steroid named as albosteroid showed considerable ($P<0.05$, $P<0.01$ and $P<0.001$) antiulcer activity in the models (pylorus-ligation- and ethanol-induced ulcer models) [4].

***2.* Anti-Diabetic Activity of M. alba**

The study reports the experiments carried out on groups of rats with control group, diabetic group, control treated with *M. alba* group and diabetic treated with *M. alba* after STZ-induced diabetes group for the study of effects of *M. alba* on peroxidation of lipids and enzymes regulates the glucose in streptozotocin (STZ). The results during the study showed a significant increase in peroxidation of lipid in diabetic group while the diabetic rats treated with *M. alba* showed reduced lipid peroxidation. This study also revealed that the diabetic rats treated with *M. alba* also prevented by glycogen depletion and overproduction of lactate avoided with considerable scale as by other groups. Also the hexokinase, glucose 6 phosphate dehydrogenase and lactate dehydrogenase activities also increased in diabetic rats treated with *M. alba* while glutathione s transferase and glucose 6 phosphatase activity decreased. This study showed the diabetic rats treated with *M. alba* improve hepatic carbohydrate metabolism, reduce hyperglycemia by control oxidative stress and increasing the glycogen levels, prevent anaerobic glycolysis and reduce blood glucose levels by regeneration of β cells[10, 11,30]. The extract of leaves of *Morusalba* also showed considerable beneficial results for type II diabetic rats[23]. The study also showed *M. alba* suppresses the blood glucose level by intestinal disaccharidase activity inhibitory effects that used extract of leaves of mulberry containing 0·24% 1-deoxynojirimycin[38]. The regulation of hypoglycemic condition also can achieved by using mulberry as investigation suggested[41].

3. Anti-obesity Activity of M. alba

The study reported isolation of compound containing arabinan and arabinogalactan (AG II) side chains and the use as anti-obesity agent. The apoptotic death studied by stimulation of MAPKs (ERK and p38) signalling pathway. The results shows the compound show inhibition of preadipocyte proliferation by reducing the fat cells as well the adipose tissues. This study revels this compound in *M. alba*can be used as functional ingredient in health beneficial foods[12]. Further studies also reported the regulation of oxidative stress in the liver and hyperglycemia as well in obese mice by dietary consumption of *M. alba*[30,33]. Investigation regarding proliferation and differentiation of 3T3-L1 preadipocytes also showed inhibition of proliferation and differentiation[47].

4. Anti-cancer Activity of M. alba

The study reported the isolation of morusin and a flavonoid structure elucidated as 3′-geranyl-3-prenyl-2′,4′,5,7 tetrahydroxyflavone by using spectroscopic techniques and the cytotoxicity of

compound tested against human breast carcinoma MCF-7, human hepatocarcinoma Hep3B cells and human cervical carcinoma HeLa. That isolated compound showed great results against respective tests[14]. Furthermore in vitro study showed the extract of root and bark of *M. alba*induce cell death and growth limitation in human colorectal cancer cells[17]. Extract of leaves of mulberry are also investigated by its beneficial effect in case of hepatocellular carcinoma (Liver cancer) by starting caspases, inhibited activity of topoisomerase IIα, in the G2/M phase induced cell cycle arrest all this action to HepG2 hepatoma growth inhibition[37]. *M. alba*also reported inhibitory to HO-8910 cells' proliferation human ovarian cancer [48].

5. Antiviral Activity of M. alba

Number of isolated from root bark of *Morus alba L* including a-acetyl-amyrin, leachianone G, oxydihydromorusin, eudraflavone B hydroperoxide, a prenylated flavonoid, moralbanone, cyclomorusin, mulberroside C and kuwanon S their structures were determined using spectroscopic techniques and tested for antiviral effect. Compounds showed goods results by against herpes simplex type 1 virus (HSV-1) mulberroside C showed weak activity (IC50=75.4 mg/ml) while Leachianone G showed potent antiviral activity (IC50=1.6 mg/ml) against herpes simplex type 1 virus (HSV-1)[16]. Mulberry also found handy for treatment of foodborne viral infection as investigated effects on feline calicivirus-F9 (FCV-F9) and murine norovirus-1 (MNV-1) with juice of *M. alba.* That resulted reduction of polymerase gene expression of MNV-1 that inhibited viral replication[35].

6. Anti-inflammatory of Activity M. alba

To study the anti-inflammatory the griess method used to measure NO while Western blot technique used to analyze proteins regulation NF-κB and ERK1/2 signal. The root and bark extract of *M. alba* showed anti-inflammatory effect by blocking production NO by suppressing iNOS, also by blocking IκB-α degradation and ERK1/2 activation inhibited NF-κB activation through p65 nuclear translocation by its hyper-phosphorylation[17]. Moreover the experiment on rats to test the anti-inflammatory effects of oxyresveratrol and mulberroside A, compounds extracted from *M. alba*used the carrageenin-induced model of inflammation. Compounds Mulberroside A and oxyresveratrol considerably showed effects to reduced paw edema in rats[18]. Kuwanon G isolated from *M. alba* also showed Anti-inflammatory effect during investigation. It reduces the inflammatory cells of asthmatic mice in in the BAL fluids[24]. For treatment of airway inflammation *M. alba*proven a right choice as report suggested as results of an experiment performed on mice[36].

7. Anticonvulsant activity of Activity M. alba

New compound from *M. alba*Morusin was isolated to study anticonvulsant activity using maximal electroshock (MES)-induced convulsion and isoniazid (INH) models. Observing the GABA level in the brain the biochemical mechanism was investigated. The dose (LD_{50}) of Morusin used up to 20 mg/kg. The level of GABA in rats brain increased it shows the anticonvulsant activity of Morusin[20].

8. Hepatoprotective Activity of M. alba

Study reports the isolation of moralbosteroid from *Morusalba*and tested against hepatoprotective activity in wistar albino rats induced by CCl_4. Results showed a great influence of moralbosteroid to prevent liver toxicity induced by CCl_4 in rats. It inhibited the processes of free radical simply by scavenging of hydroxyl radicals and marked escalation of serum were prevented, it also increased the antioxidant enzyme levels in hepatocellular and regulated the LPO levels[21]. *M. alba* also found hepatoprotective effects on oxidative stress in HepG2 t-BHP oxidative stress induced cells[25]. In case of liver cancer (hepatocellular carcinoma) mulberry also found useful. Results shows the inhibition of HepG2 hepatoma cells growth and activation of cell apoptosis[37].

9. Anti-adherence activity of M. alba

The study conducted to isolate a compound from *M. alba*characterized as 1-deoxynojirimycin for inhibition of *Streptococcus mutans* biofilm formation. Crude extract of leaves of *M. alba* tested against *Streptococcus mutans*. By using micro dilution method the MICs were observed. The compound separated and purified by mean of chromatographic methods and characterized by spectroscopic techniques, biofilm formation and adherence of *S. mutans* were

evaluated with sub-MIC concentrations of extract and then by pure compound. Polysaccharide secretion on the extracellular side of *S. mutans* effects by pure compound using both water and alkali soluble polysaccharide were studied, and using confocal microscopy effect on biofilm architecture was also observed. Investigation of *S. mutans* revealed the pure isolated compound had an 8-fold good reduction of MIC as compared to crud extract (MICs, 15.6 and 125 mg/L, respectively). Even the biofilm formation of *S. mutans* strangely inhibited at active stage of accumulation and plateau. The 1-deoxynojirimycin was found 22% more effective for reduction in alkali soluble rather than water soluble polysaccharide. The results reveled that *M. alba is* effective to control the overgrowth and biofilm formation of *S. mutans*[22].

10. Anti Asthmatic Activity of M. alba

*M. alba*found as good anti asthmatic remedy when study carried out on mice induced with allergic asthma. The mice treated with Kuwanon G compound isolated from root bark of *M. alba*for 7 days. In sera Th2 cytokines and OVA-specific IgE levels were observed and changes in tissues as well. In the BAL fluid and sera of asthmatic mic the OVA-specific IgE and IL-4, IL-5, and IL-13 decreased significantly and remove number of inflammated cells, epithelium of bronchioles thickened and also inhibited the accumulation of collagen and mucus. These results suggested that *M. alba*hadgreat influence regarding allergic asthma[24]. Mulberry also found useful for treatment of lungs inflammation as airway inflammation including bronchitis[36].

11. Antioxidant Potential of M. alba

M. alba poses a great antioxidant potential confirmed during the investigation the three compound quercetin 3-(6-malonylglucoside), rutin (quercetin 3-rutinoside) and isoquercitrin (quercetin 3-glucoside) from leaves of *M. alba* isolated and tested to prevent the LDL from oxidation. Results showed the inhibition LDL oxidation that was induced by Cu ion[15, 26]. Apart from this thealbosteroid compounds isolated from mulberry also been proven as antioxidant during the investigation of antiulcer effects of *M. alba*[4]. Further studies also suggested that to maintain the antioxidant activity of *M. alba*temperature play very important role. A strict temperature maintenance is necessary for maintenance of antioxidant activity of compounds to isolate and to achieve significantly better results[28, 29], and also water stress dependent as well[40], ethanolic extracts of mulberry showed stronger effects as compared to aqueous extracts[45].

12. Antibacterial Activity of M. alba

The number of studies proven the mulberry as an antibacterial.*M. alba* showed successful results about inhibition of biofilm in *Streptococcus mutans* during the active stage of accumulation and plateau, the compound 1-deoxynojirimycin (DNJ) was isolated was the compound showed these results[22, 39]. *M. alba*also showed great influence to use with other antibiotics showed excellent results in that way. It is very helpful for making strategies regarding antibiotics[3]. During an other study isolated compounds sophoraisoflavanoneA, sophoraflavanone D, papyriflavonol A and kuraridin from *M. alba* showed good antifungal and antibacterial characteristics against *S. aureus*, *Staphylococcus epidermis*, *Salmonella typhimurium* and *Escherichia coli*[42]. Ethanolic extract from leaves of mulberry also proven its anti-bacterial effects on bacterial species *Pseudomonas aeruginosa* and *Staphylococcus aureus* in a study[43].

13. Anti-melanogenesis Activity of M. alba

Extract of leaves of *M. alba*found very good results for the treatment of melanogenesis during investigation and isolation of active constituents from *M. alba.* During the *in vitro* study of isolated compounds using mushroom tyrosinase and in B16F10 melanoma cells observing the melanin content, study revealed the influence of *M. alba*for inhibition activity on tyrosinase and also increased melanin synthesis with α–MSH. This study further encourage the investigation of *M. alba* regarding skin pigmentation[27].

14. Macrophage activating Activity of M. alba

The benefits of *M. alba* regrinding macrophage reported in study, that reveled the macrophage activating nature of number of compounds as pyrrole alkaloids, Morrole A, 5-(hydroxymethyl)-1H-pyrrole-2-carboxaldehyde, 2-formyl-5(methoxymethyl)-1H-pyrrole-1-butanoic acid, 2-formyl-5-(hydroxymethyl)-1H-

pyrrole-1-butanoic acid and 2-formyl-1Hpyrrole-1-butanoic acid isolated from *M. alba* and macrophage activity evaluated by nitric oxide production. Nitric oxide, TNF-a and IL-12 production enhancement and phagocytic activity stimulation in RAW 264.7 cells showed the macrophage activating nature of*M. alba*[31].

15. Melanin Biosynthesis Inhibitory Activity of M. alba

Experiment conducted for investigation of *in vitro* effects of methanol extract (85%) of dried leaves of mulberry on biosynthesis of melanin. Mulberroside F (moracin M-6, 3-di-O-b-D-glucopyranoside) inhibited tyrosinase activity which is responsible for the conversion of dopachrome from dopa during melanin biosynthesis. These results proven the effects of *M. alba*as skin whiting raw material as poses mulberroside F[32].

16. Anti-Hyperlipidemia Activity of M. alba

Anti-hyperlipidemia activity of *M. alba* tested in investigation using mixture of three herbs *Artemisia capillaries* (Thunb), *Melissa officinalis* L. (Labiatae) and *Morus alba* L. (Moraceae) on mice for 12 weeks fed a high-fat diet that gained weight and mice fed a low fat diet. The mice fed with high fat diet and mixture of herbs did not gained weight as much mice not fed with herbs mixture but fed with high fat diet. Using herb mixture regulated lipid metabolism, adiposity and weight gain. Not only this herbs treatment also inhibited the hepatic lipid accumulation and decreased the triglycerides and total cholesterol circulating levels. These results are quite helpful to understand the influence of *M. alba*regarding hyperlipidemia[33]. Investigation of hypolipidemic effect of *M. alba*on rats also reported the liver triglyceride and serum levels, atherogenic index and low-density lipoprotein cholesterol decline, at the same time increased the high-density lipoprotein cholesterol[46].

17. Cardioprotective Activity of M. alba

In traditional Chinese medicine *Morusalba*used to treat number of diseases as expectorant, headache, diuretic, diabetes and many more. In recent days regarding *M. alba*the study conducted to investigate its*in vitro* and *in vivo* effects to cardiovascular disorders as Thromboxane B2 and Thrombus formation respectively. Morusinol extracted from mulberry, antiplatelet potential tested on rabbit by *in vitro* platelet aggregation and Thromboxane B2 formation assays. *In vivo* investigation of formation of arterial Thrombus induced thrombosis model of ferric chloride ($FeCl_3$). Results were quite surprising as expected, platelet aggregation, collagen TXB2formation inhibited by morusinol. Thrombus formation for collagen-induced TXB_2 99% and for arachadonic acid-induced TXB_2 formation for 29.2% reduced. These results showed morusinol had good potential for treatment of cardiovascular diseases as investigated[34]. Studies also reveled in addition to extract of *M. alba*using Monacolin K and Berberin can improve the glucose metabolism and plasma cholesterol regulation. Which be helpful in cardiovascular diseases[44].

18. Antifungal Activity of M. alba

Prenylated flavonoids from different medicinal plants including *M. alba*isolated and tested against two fungal species *Candida albicans* and *Saccaromyces cerevisiae*one the isolated compounds sophoraisoflavanone A, sophoraflavanone D, kuraridin and papyriflavonol A showed good antifungal characteristics and antibacterial as well[42]. In another investigation of toxicity of *M. alba*on mice also revealed the antifungal activity of an ethanolic extract from leaves of mulberry to many fungal species as *Aspergillus flavus*, *Candida tropicalis*, *Candida krusei* and *Candida albicans*[43].

Classification of M. alba[49]
Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Hamamelididae
Order: Urticales
Family: Moraceae
Genus: Morus L.
Species: Morusalba L.

Common names

Mulberry, Silkworm mulberry, Shahtoot (Urdu).

Table 1: Presenting various chemical constituents of plant Morusalba

Chemical Compounds	Parts	References
Protein	Leaves	2, 54
Fat	Leaves	2
Fatty acids	Different parts of plants	13
Amino Acids	Fruit	53
Carbohydrate	Different parts of plants	4
Fibre	Leaves	2
Ash content	Leaves	2
Saponin	Leaves	2, 4
Alkaloids	Leaves, fruits	2, 4, 59
Nortropane Alkaloids	Fruit	53
Flavonols	Different parts of plants	6, 13, 14, 51
Flavonoids	Leaves	2, 3, 4, 8
Flavan	Fruit, Leaves	55, 60
Coumarin	Bark	57
Terpenoids	Different parts of plants	4, 9
Tannins	Leaves	2, 4
Phytate	Leaves	2
Anthraquinone Steroids	Different parts of plants	4
Octadecanol	Leaves	5
Polysaccharide	Different parts of plants	12
4-hydroxy octadec-6	Leaves	5
9-dienoic acid	Leaves	5
β-sitosterol	Leaves	5
Stigmasterol	Leaves	5
Protocatechuic acid	Different parts of plants	6
Vanillic acid	Different parts of plants	6
Benzoic acid derivatives & derivatives	Different parts of plants	6, 55, 56
Chlorogenic acid	Different parts of plants, fruit	6, 55
Caffeic acid	Different parts of plants	6, 13, 55, 56
Coumaric acid	Different parts of plants	6, 55
Ferulic acid	Different parts of plants	6, 55
Gallic acid	Fruits	55
Ellagic acid	Fruits	55
Gentisic acid	Fruits	55
Total cinnamic acid derivatives	Different parts of plants	6
Quercetin	Different parts of plants	6, 58
Kaempferol	Different parts of plants	6, 58
Rutin	Different parts of plants	13, 52, 55
Citric acid	Fruit, Leaves	50, 56
Tartaric acid	Fruit	50
Malic acid	Fruit, Leaves	50, 56
Quinic acid	Leaves	56
Succinic acid	Fruit	50
Lactic acid	Fruit	50
Fumaric acid	Fruit	50
Acetic acid	Fruit	50
Benzofuran	Bark	57
2-arylbenzofuran derivatives	Root bark	51, 56
Maclurin	Root bark	52
Isoquercetrin	Root bark	52
Resveratrol	Root bark	52
Trypsin inhibitor	Leaves	2
Calcium	Leaves	2
Phosphorus	Leaves	2
Zinc	Leaves	2
Potassium	Leaves	2
Magnesium	Leaves	2
kuwanon G	Leaf	3
Morusin U	Leaf	3

Oxyresveratroldihexoside	Leaf	3
OxyresveratrolMoracin M	Leaf	3
Moracin P pentoside	Leaf	3
Moracin P	Leaf	3
Moracenin D	Leaf	3
Mulberrofuran C	Leaf	3
Kuwanon L	Leaf	3
Albanin A	Leaf	3
Kuwanon O	Leaf	3
Cyclocommunol	Leaf	3
Morusinol	Leaf	3
Kuwanon H	Leaf	3
Sanggenol M	Leaf	3
Kuwanon C	Leaf	3
Kuwanon A	Leaf	3
Kuwanon F	Leaf	3
Kuwanon B	Leaf	3
Morusin	Leaf	3
Kuwanon B	Leaf	3
Kuwanol C	Leaf	3
Hydroxymorusin	Leaf	3
Wittifuran B	Leaf	3
Cyclomorusin	Leaf	3
Glycosides	Different parts of plants	4, 57
Stilbene	Bark	57
Mulbaines	Fruits	59

Table 2: Presenting various pharmacological activities attributed to plant M. alba

Activity	References
Hepatoprotective	25, 37
Hypoglycemic	33, 46
Anti-Ulcer	4
Anti-inflammatory	17, 18, 24, 36
Antioxidant	4, 15, 26, 28, 29, 40, 45, 52
Antifungal	42, 43
Antibacterial	3, 22, 39, 42, 43
Anti-diabetic	10, 11, 23, 30, 41
Anti-convulsant	20
Anti-Asthmatic	24, 36
Anti-Cancer	17, 37, 48
Anti-obesity	12, 30, 33, 47
Anti-viral	16, 35
Anti-adherence	22
Anti Melanogenesis	27
Macrophage	31
Skin caring	32, 27
Cardioprotective	34, 44

Fig. 1: Root of M. alba

Fig. 2: Flower of M. alba

Fig. 3: Whole plant of M. alba

Fig. 4: Fruit of M. alba

Fig. 5: Leaves of M. alba

Fig. 6: Stem of M. alba

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