

Anti-obesity and Hypolipidemic Effects of *Morus alba*- A Review

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Abstract

The prevalence of obesity was worldwide increase in the last 60 years. Obesity represented one of the public health problems, it markedly increased the incidence of many diseases: fatty liver, type 2 diabetes, hypertension, ischemic heart diseases, sleep apnea, osteoporosis, dementia, tumors and many other disorders. Recent reviews showed that many medicinal plants possess anti-obesity effect. In the current review, PubMed, Web Science, Science Direct, Researchgate, Academia.edu and Scopus were searched to verify the hypolipidemic and anti-obesity activities of *Morus alba*.

Key words: Anti-obesity, overweight, hypolipidemia, *Morus alba*, Review

Introduction

The prevalence of obesity was worldwide increase in the last 60 years. Obesity represented one of the public health problems, it markedly increases the incidence of many diseases: fatty liver, type 2 diabetes, hypertension, ischemic heart diseases, sleep apnea, osteoporosis, dementia, tumors and many other disorders. Therefore, it deteriorated the quality of life. Behavioral interventions and lifestyle changes aimed to increase energy expenditure and reduce the caloric intake showed limited efficacy because of complex etiology (hormonal, metabolic, and neurochemical). Many drugs were also used to suppress their appetite and avoid overeating⁽¹⁾. In the current review, PubMed, Web Science, Science Direct, Researchgate, Academia.edu and Scopus were searched to verify the hypolipidemic and anti-obesity activities of *Morus alba*.

Morus alba

Morus alba (Family: Moraceae) fruits were used traditionally as anthelmintic, antibacterial, sedative,

analgesic, antirheumatic, diuretic, hypotensive, hypoglycemic, purgative, restorative, tonic, and hypolipidemia⁽²⁻⁶⁾. The phytochemical analysis showed that the plant contained tannins, steroids, phytosterols, sitosterols, glycosides, alkaloids, carbohydrates, proteins and amino acids, flavanoids, phenolics, anthocyanins, anthroquinones, saponins, triterpenes, and glycosides⁽⁷⁻¹⁰⁾. The fruits contained protein 1.55g, lipids 0.48g, crude fiber 1.47g; and total carbohydrates 14.21g/100g dry weight. The Total sugar content was 7.55g, ascorbic acid 15.2mg, riboflavin 0.088mg, niacin 3.10mg/100 g fresh weight. The total phenolic contents was 7.7 to 11.2mg GAE/g, and total flavonols 0.07 to 0.51 mg/g dry weight⁽¹¹⁾. The elements and minerals detected in the fruits were: N 1.62-2.13, P 0.24-0.31, K 1.62-2.13, Ca 0.19-0.37, Na 0.01, Mg 0.12-0.19, S 0.08-0.11g/100 g. While, the fruits contained Fe 28.2-46.74, Cu 4.22-6.38, B 13.78-19.48, Mn 12.33-19.38, Zn 14.89-19.58 and Ni 1.40-2.62 mg/kg⁽¹²⁾.

The freeze-dried powder of mulberry fruits contained phenols 23.0mg/g GAE, flavonoids 3.9

mg/g rutin equivalents and anthocyanins 0.87mg/g cyanidin-3-glucoside equivalents. Rutin (0.43mg/g), morin (0.16mg/g), quercetin (0.01mg/g) and myricetin (0.01mg/g) represented the main flavonol in the fruit powder⁽¹³⁾.

However, anthocyanins content of the fruit ethanol extract was 137 to 2057 mg malvidin-3-glucoside equivalents/kg⁽¹⁴⁾. Anthocyanins isolated from the fruits included cyanidin 3- glucoside, cyanidin 3-*O*- β -D-glucopyranoside, cyanidin 3-rutinoside, cyanidin 3-*O*-(6-*O*- α -rhamnopyranosyl- β -D-glucopyranoside), cyanidin 3-*O*-(6-*O*- α -rhamnopyranosyl- β -D-galactopyranoside), cyanidin 3-*O*- β -D-galactopyranoside and cyanidin 7-*O*- β -D-glucopyranoside⁽¹⁵⁻¹⁶⁾.

Flavonoids identified in the fruits were astragalin, nicotiflorin, quercetin, isoquercitrin, morkotin A and C, rutin, kaempferol 3-*O*-(6-*O*-malonyl) glucoside, kaempferol 3,7-di-*O*-glucoside, quercetin 3, 7-di-*O*-glucoside and quercetin 3-*O*-(6-*O*-malonyl) glucoside⁽¹⁷⁾. The total phenolic contents of *Morus alba* leaves were 2.64 to 7.33 mg GAE/g dry weight and total flavonoids were 0.95 to 2.39 mg QE/g dry weight. The polyphenols isolated from the fruits and leaves of *Morus alba* were: gallic acid, caffeic acid, chlorogenic acid, *m*-coumaric acid, *p*-coumaric acid, ferulic acid, vanillic acid, *p*-hydroxybenzoic acid, protocatechuic acid, syringic acid, protocatechuic aldehyde, syringaldehyde, kaempferol, epicatechin, and rutin⁽¹⁸⁻¹⁹⁾.

The previous pharmacological researches showed that *Morus alba* exerted protective, neural, anti-inflammatory, antimicrobial, analgesic, antipyretic, musculo-skeletal, immunological, antioxidant, antidiabetic, anticancer, cardiovascular, dermatological, gastrointestinal and respiratory therapeutic effects.

Hypolipidemic and anti-obesity effects:

The antioxidant and hypolipidemic activities of the root bark fractions of *Morus alba* were studied in rats fed high cholesterol diet. The results revealed that the administration of (50% methanol and 100% methanol) fractions ameliorated atherosclerotic state. Administration of 100% methanol fraction markedly restored the liver and plasma peroxides to normal limits, and significantly increased the resistance to atherogenic changes (44, 33, and 30% reduction in the LDL oxidation, LDL retention and LDL aggregation, respectively). Mulberroside A, albanols A and B and 5,7,2'-trihydroxyflavanone-4'-*O*- β -D-glucoside were identified in the root and bark fractions⁽²⁰⁾.

Mulberry leaves extract caused marked decline in the triglycerides, LDL cholesterol and total cholesterol, and increased the serum level of HDL cholesterol in rats and mice⁽²¹⁻²⁵⁾.

The aqueous extract of Mulberry leaves at a dose of 150 mg/kg/day, for 14 days, significantly decreased the triglycerides level by 55.01% in rats on high cholesterol diet⁽²⁶⁾.

Morus alba leaves ethanol extract markedly decreased body weight gain, and diminished the elevated cholesterol, triglycerides, atherogenic index and coronary artery indices, it also decreased insulin resistance and glucose level in hyperlipidemic rats induced by high-cholesterol diet (HCD). The serum leptin and resistin and their mRNA expression in visceral adipose tissue were significantly decreased by the extract, while, it increased serum adiponectin, and its expression significantly in visceral adipose tissue in hyperlipidemic rats⁽²⁷⁾.

Mulberroside A (MUL), the pure root ethanolic extract of Mulberry, and oxyresveratrol (OXY), prepared from MUL enzymatically, were studied (1-5mg/kg/day, for 4 weeks) for their hypolipidemic effect in high cholesterol diet (HCD)-

induced hyperlipidemic, in triton WR-1339-induced hyperlipidemic rats, and normal rats. Triton-induced hyperlipidemic rats pretreated with MUL and OXY orally, showed decreased levels of serum lipids significantly. MUL and OXY in HCD-fed rats caused significant decline in lipids and atherogenic index. In addition, MUL and OXY induced significant ameliorated the histological hepatic changes in HCD hyperlipidemic rats. Liver enzymes values were not significantly different in OXY-treated normal rats compared to water-treated rats⁽²⁸⁾.

The accumulation of lipid in the liver was decreased by *Morus alba* leaves extract, the number and the size of lipid droplets in hepatocytes were significantly less than that in the control^(22,24).

Flavonoids, phenolics and 1-deoxyojirimycin, isolated from the leaves of mulberry decreased plasma lipids by many mechanisms as detected by in vitro and in vitro experiments. Kaempferol, quercetin, and 1-deoxyojirimycin enriched leaves extracts activated the expressions of AMP-activated protein kinase and PPAR- α , and increased lipid breakdown and free fatty acid β -oxidation^(23,29).

The leaves extract rich in polyphenol (quercetin, hydroxyflavin and caffeic acid) reduced lipogenesis by regulating of glycerol-3-phosphate acyltransferase, fatty acid synthase, liver X receptor and sterol regulatory element-binding proteins-1c^(24, 30-31).

Moracin isolated from the leaves of *Morus alba* inhibited lipid peroxidation which strongly indicated its role as scavenger⁽²⁶⁾.

The antioxidants and hypolipidemic effects of the fruits of *Morus alba* were studied in hypercholesterolemic rats. The fruits of *Morus alba* at doses of 2.5, 5 and 10% caused significant increase in **the antioxidant activity** and significant decrease the total cholesterol, triglycerides, VLDL, and LDL cholesterol, with significant elevation in HDL

cholesterol.⁽³²⁾

The effects of mulberry leaves extract fermented by *Cordyceps militaris* for 12 weeks, on the lipolytic activity, metabolism and accumulation of the lipids were measured in obesity induced in mice by high fat diet (HFD). The levels of total cholesterol, triglyceride, LDL cholesterol, and glucose were significantly decreased, and the level of HDL-cholesterol was significantly increased in high fat diet (HFD) + extract treated group compared with the HFD group treated with vehicle. The size of adipocytes and the amount of abdominal fat were significantly decreased. The mRNA levels of (PPAR γ) for adipogenesis in addition, Fas cell surface death receptor and adipocyte protein 2 were decreased after 12 weeks treatment with the extract⁽³³⁾.

The effect of Ob-X, (contained: *Artemisia capillaries*, *Morus alba* and *Melissa officinalis*) on angiogenesis was determined by mice Matrigel plug assay. Ob-X decreased the angiogenesis dose-dependently. Ob-X for 5 weeks in mice caused 27% reduction in bodyweight gain. Furthermore, the visceral adipose tissue and the size of adipocytes in visceral adipose were decreased by 46 and 15%, respectively. In addition, the treatment also significantly decreased the hepatic accumulation of lipids and the blood glucose levels⁽³⁴⁾.

The effect of leaves extract on oxidative stress induced by obesity, in addition to its effect on lipogenesis, hepatic fibrosis, was investigated in obese mice fed high-fat diet (HFD). The extract significantly decreased LXR α -mediated lipogenesis and hepatic fibrosis markers and up-regulated lipolysis-associated markers. Moreover, the extract restored the antioxidant enzymes activities in the HFD-fed mice⁽³⁵⁾.

The benefit of synergism between β -glucan and the leaf extract of mulberry on metabolic health were studied in mice fed high fat diet. β -glucan administration

significantly decreased lipid profile, fat mass, fatty liver, body weight gain, insulin, and inflammatory markers. On the other hand, the administration of mulberry leaf extract possessed an efficacy similar to that of β -glucan (Except the effect on weight gain). Furthermore, a mixture of β -glucan and mulberry leaf extract showed synergism in improvement of insulin sensitivity⁽³⁶⁾.

The effect on food intake and weight of flavonoid standardized extract of *Morus alba* were evaluated in diet-induced obesity in the mice. The extract significantly and dose-dependently reduced the food intake in acute and prolonged treatment. The extract (250mg/kg) decreased food intake by 58.6% and 44.8% and at a dose of 500mg/kg decreased food intake by 50.1% and 44.3% at 1 and 2 h after extract treatment. The high *Morus* root-bark extract dose caused 16.5 and 22.5% loss in body weight at baseline and week 7, respectively, in obese mice with marked decrease in visceral fat deposit and biochemical markers⁽³⁷⁾.

JS-MP-1, a polysaccharide identified in *Morus alba* significantly decreased 3T3-L1 pre-adipocyte cells viability, reduced the ratio of the expression level of Bcl-2/Bax which induced dysfunction of mitochondria and preadipocyte cells apoptosis, and stimulated the cleavage of caspases 3 and 9 and poly polymerase. The apoptotic death appeared to be mediated by ERK and p38 signalling stimulation, which indicated that the polysaccharide was able to decrease the adipose tissue mass and the fat cells number via inhibition of proliferation of preadipocyte⁽³⁸⁾.

The anti-adipogenic and antioxidant effects of *Nelumbonucifera Morus alba* and *Raphanus sativus* mixture were studied. The mixture decreased body, adipose tissue and liver in high-fat diet. It decreased the glucose and lipid profile elevated by high fat diet. Blood glucose and serum insulin growth factor-1, leptin and non-esterified fatty acid, were significantly declined, while, serum adiponectin was increased

significantly⁽³⁹⁾.

When the 3T3-L1 cells treated by *Morus alba* ethanolic extracts at 100 microg/ml, the adipocyte differentiation was decreased by 18.6%. It decreased C/EBP α expression and suppressed mRNA of PPAR γ in 3T3-L1 cells. A highest antiadipogenic effect on 3T3-L1 cells was induced by ethyl acetate fraction. At a concentration of 100 microg/ml, the fraction decreased lipid accumulated intracellularly by 38.5%. Protocatecholic acid which identified in the fraction, at a concentration of 100 microM, inhibited the accumulation of lipid by 44.8%, therefore the inhibition of lipid accumulation induced by the ethyl acetate fraction could be attributed to protocatecholic acid⁽⁴⁰⁾.

The pharmacological activity of UP601 (a mixture of *Morus alba*, *Yerba mate* and *Magnolia officinalis* extracts), was studied on changing of obesity-related parameters and biochemical markers in obesity induced in mice by high fructose (HFF). UP601 at a dose of 250 mcg/ml, induced a 1.8-times increase in lipolysis. UP601 decreased body weight by 9.1, 19.6 and 25.6% at doses of 300mg, 450mg and 600 mg/kg for 7 weeks in rats. The same doses caused reduction in the total cholesterol 9.1, 16.9 and 18.6%; in triglycerides 45.0, 55.0, 63.6%; in LDL 34.8, 37.1 and 41.6%; and in serum glucose 3.2, 21.6 and 33.7%, respectively. UP601 also caused 31.6% reduction in the body fat distribution and up to 89.1% decrease in the mesenteric fat⁽⁴¹⁾.

UP601 (orally, 1.3 g/kg/day, for 7 weeks) was also studied for its appetite suppression and management of metabolic disorders in mice models. It caused marked decreases in food intake 81.8, 75.3, 43.9, and 30.9% at 2, 4, 6, and 24 hours. Furthermore, it decreased body weight gain 21.5% VS 8.2%, at 7 weeks compared with untreated high fat diet-mice, decreased calorie intake 40.5% at the first week, reduced insulin and leptin by 75.9% and

46.8% , respectively, increased ghrelin level 4.2 times, and significantly decreased cholesterol and LDL. Mice treated by UP601 also showed less body fat, less mesenteric fat pad with an improvement of nonalcoholic steatohepatitis scores⁽⁴²⁾.

The acute, subacute and chronic toxicological studies in mice and rats showed that *Morus alba* was a safe remedy with high therapeutic index^(7, 43-49).

Conclusion

Morus alba possessed many therapeutic effects. The current review discuss its hypolipidemic and anti-obesity effect. *Morus alba* caused appetite suppression and exerted hypolipidemic and antiobesity effect by many mechanisms. Furthermore the toxicological studies revealed that *Morus alba* is an edible and very safe remedy. It is a promising medical therapy with wide range of pharmacological effects.

Ethics approval and consent to participate

The work is a review, the authors didn't perform experimental and clinical work.

Consent for publication

The manuscript didn't contain any individual person's data.

Competing interests

The author confirm that this paper's content has no conflict of interests.

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Author's contributions

Both authors drafted the and approved the manuscript

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