Nutritional Composition, Bioactive Compounds and Hypolipidemic Effects of Mulberry Leaves

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Abstract

Mulberry (*Morus spp.*, *Moracecae*) is a notable remedial and multi-functional plant. Distinct mulberry types are spread in subtropical, temperate and tropical areas all over the world but the plant mainly is common in China, Korea, India and Asian countries. Mulberry leaves carry a number of bioactive compounds with it along with various pharmacological effects. It is an magnificent origin of nutrients, and phytochemical and is been proven as a nutraceutical. They also act as antioxidant to prevent lipid peroxidation and oxidative stress. Mulberry leaves have a broad extent of therapeutic effects having bacteriostatic, anti-hyperlipidemia, lowering blood glucose, anti-hypertensive, and antiviral properties. The goal of this analysis is to estimate the direct action of extract of mulberry leaves on hyperlipidemic induced rats' model. The present study will contribute evidence-based results regarding the antihyperlipidemic effects of mulberry leaves. Previous studies suggest that mulberry leaves are highly effective to manage hyperlipidemia and dyslipidemia due to their lipid ameliorating and antioxidant effect.

Keywords: Mulberry leaves, Hyperlipidemia, Phytochemicals, Lipid peroxidation.

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Introduction

An overabundance of lipids (fats) in the blood is referred to as hyperlipidemia, such as triglycerides and cholesterol. Hypercholesterolemia is a kind of hyperlipidemia in which your blood has an abnormally high level of LDL cholesterol and non-HDL cholesterol. As a result of this illness, fatty deposits form in the arteries, increasing the risk of blockages (18). In the vast majority of cases, hyperlipidemia is classed as primary; it is also known as familial because a genetic fault causes it; it can be monogenic or polygenic. Other illness, such as diabetes, nephritic syndrome, persistent alcoholism, hypothyroidism, and medicines such as corticosteroids, beta-blockers, and oral contraceptives, causes the secondary (37). CVD is the most frequent noncommunicable illness in the world, accounting for around 31% of all deaths. In the future years, the number of fatalities from cardiovascular illnesses will rise from 14.4 million to 17.5 million globally.

In 2015, it was expected to reach around 20 million. 3 The condition affects around 3.5 million people in Europe. CVD has declared the lives of 2.7 individuals in millions from US, while the disease has claimed the lives of 29 percent of people in Pakistan. A higher risk of heart disease is connected to high cholesterol levels. Stroke, Coronary heart disease, and peripheral vascular disease are only a few examples. High blood pressure Diabetes and have also been linked to high cholesterol (2). Atherosclerosis, myocardial infarction (MI), ischemic stroke, and coronary artery disease are all caused by hyperlipidemia. Excessive alcohol consumption, the use of hormones or steroids, obesity, diabetes, and metabolic syndrome are all factors that contribute to metabolic syndrome. Hyperlipidemia can be caused by a number of causes, including early menopause, an underactive thyroid gland, long-term renal disease, hypothyroidism, pregnancy, and a sedentary lifestyle.

Mulberry Plant

Morus nigra L., sometimes known as mulberry's leaf, is a type of Traditional Chinese Medicine (TCM) is a sort of Chinese medicine that has been practiced for thousands of years in clinical settings. Mulberry is a well-known herbal remedy (*Morus spp.*, *Moraceae*). Mulberry species can be found all over the world in subtropical, tropical, and temperate settings.

However, the majority of the plant's distribution is in Japan, Korea, China, and India. The red mulberry, black mulberry, and white mulberry are the most famous Morus species that belong to the genus *Morus rubra*. The mulberry leaf contains recognized amino acids, flavonoids, vitamins, minerals, and other active substances. Mulberry is a shrub with several uses (31) . Mulberry has made a name for itself as a useful food due to its high content of minerals and phytochemicals (26). Fresh fruits are harvested and used in a variety of food products, including jelly, jam, and juice. Mulberry leaves are essential in the sericulture sector since they are the only food source for the silkworm (13; 26). Because of the beneficial influence on milk production. The leaves are often utilized in the feed for dairy animals.

Mulberry leaf herbal tea is popular in Asian nations as a nutritious beverage. The mulberry tree's leaves, roots, bark, and fruits were used to treat coughs, fevers, hyperlipidemia, hypertension, and hyperglycemia have all been treated with them in traditional medicine for a long time. Mulberry leaves are light green in color and are slender and glossy. Even within the same tree, the leaf shape might vary considerably. Some leaves have five lobes, whereas others have one, two, three, or none. Despite the fact that the vast majority of genuine black mulberry trees are broad, low and usually like the tree of apple which is small in size, with the length of 51 feet tall (4).

Peroxisome proliferator-activated receptor and Activated protein kinase activation expression by Mulberry leaf extract rich in DNJ, quercetin, and kaempferol resulted in an increase in free fatty acid -oxidation and lipid breakdown. Mulberry fruit extract has also been shown to prevent Atheroma formation plaques in rabbits fed a high-cholesterol diet.

Mulberry is an edible fruit that has been used for centuries to heal fevers, protect, strengthen joints liver, and control blood pressure. To promote human health, this product can be utilized in either dry or liquid form. For better compliance, the flavor of This herbal bent can be made with or without sugar and created with FDA-approved natural ingredients. More study is needed to develop herbal mixtures for the treatment of various ailments (14).

Table 1. Proximate Analysis of Mulberry Leaves

Treatments	Moisture %	Protein %	Fat %	CHO %	Fiber %	Ash %
T1	5.2	18.40	6.46	28.37	25.12	8.7
T2	6.5	19.74	5.14	26.87	23.30	9.10
T3	4.3	24.61	4.21	27.37	20.15	11.71

Nutritional Composition

Total flavonoids, Total phenolics in mulberry leaves were measured quantitatively to be 26.42-32.27 mg equivalent to rutin and 16.20-23.36 mg equivalent to gallic acid per gram respectively. 8 Mulberry leaves are high in macro-and micronutrients, as well as organic acids. The leaves are high in protein in general. Mulberry leaves have a substantially greater protein content than other green leafy vegetables. Mulberry leaves are also high in ascorbic acid and minerals. The most abundant elements are calcium and potassium, with sodium being less abundant. Antinutritional components such as cyanide, fiber, and tannin were also discovered in the leaves of mulberry in the range of 1.01–2.14 mg/kg, 8.74–13.70 percent, 3.54–5.32 mg/kg, respectively (Thaipitakwong *et al.*, 2018).

Mulberry leaves include 2.09- 7.92% fat, 27.60-43.6% neutral dietary fiber (NDF), 15.31-30.91% protein, 11.3-17.24 % ash, 9.9-13.85 percent crude fiber, and according to studies. Vitamins, Sugars, amino acids, rutin, quercetin, volatile oil, and microelements found in mulberry leaves have a wide range of pharmacological effects having bacteriostatic, anti-hyperlipidemia, lowering blood glucose, anti-hypertensive, and antiviral properties. Different types of mulberry have

bioactive substances that can help people live longer. Mulberry tree branches have the best flavonoid-scavenging properties. Meanwhile, the flavonoid tender leaves and the content of leaves were 67.5 percent and 46.5 percent, respectively (25).

The proximate composition values for fresh mulberry leaves ranged from 4.72 to 9.96% crude protein, 71.13 to 76.68 % moisture, 8.01 to 13.42 percent carbohydrate, 4.26 to 5.32 percent total ash, 8.17 to 11.30 percent Neutral Detergent Fiber,0.64 to 1.51 percent crude fat, and 68 to 85 kcal/100 g energy. The powder of leaf of dried mulberry measured from moisture content 5.11 to 7.24 percent carbohydrate from 9.70 to 29.64 percent, with total ash ranging from 14.59 to 17.24 percent, crude fat from 2.09 to 4.93 percent, NDF from 27.60 to 36.66 percent, crude protein from 15.31 to 30.91 percent, and energy from 112 to 223 kcal/100 g. Carotene and vitamin C levels in mulberry fresh leaves were from 160 to 280 mg/100 g and 10,00.00 to 15,678.00 per 100 g, whereas leaf powder of dry mulberry had 150 to 250mg/100 g and 8427.0 to 15,135.0 per 100 g. Leaves of mulberry which are fresh had zinc, iron, and calcium concentrations of 0.21–1.14 mg per 100 g, 4.60–11.37 mg/100 g, 381–776 mg/100 g, respectively, and dried mulberry leaf powder had 18.00–34.72 mg/100 g, 0.71–3.55 mg/100 g, and 776.56–2236.66 mg/100 g. Tannic acid concentrations in new leaf ranged from 0.04 to 0.08 percent, while moisture-less leaves pulverized had 0.14 to 0.35 percent (7).

Table 2: Mineral Content of Mulberry Leaves

Mineral	Content
Nitrogen	2.0-3.2g/100g
Phosphorus	0.2-0.4g/100g
Potassium	1.3-3.7g/100g
Calcium	1.5-3.6g/100g
Sodium	0.02g/100g
Magnesium	0.4-1.5g/100g
Sulphur	0.4-0.5g/100g
Iron	118.5-234.2mg/kg
Zinc	24.8-38.3mg/kg
Manganese	34.7-91.4mg/kg
Boron	245.0-875.1mg/kg
Copper	4.6-5.8mg/kg
Molybdenum	0.7-2.6mg/kg
Nickel	1.5-5.7mg/kg
Lead	0.2-0.5mg/kg
Carbon	35.2-40.6mg/kg/100g
Lithium	1.5-15.1mg/kg
Titanium	5.5-12.5mg/kg
Organic acids	
Citric acid	30.4-106.6mg/100g
Malic acid	42.4-7.5mg/100g

Bioactive Compounds

Alkaloids (deoxynojirimycin), Flavonoids (quercetin and its homologues), sitosterols, and polysaccharides are among the chemical constituents of mulberry leaves. The principal ingredients are quercetin and its homologue, which account for more than 1% of the total. Its active ingredient, quercetin, has been shown to lower blood lipids, lower postprandial blood glucose, reduce inflammation, and fight tumors. In a conventional clinic, The antioxidant quercetin has also influenced hepatic lipid metabolism (24). Chemical investigations revealed a variety of antioxidative chemicals. Gallic, Caffeic, protocatechuic, vanillic, syringic, p-coumaric, p-hydroxybenzoic, chlorogenic, m-coumaric and ferulic acids were found in leaves of mulberry. Izoquercitrin, Rutin, and astragalin were the flavonol chemicals found. Total flavonoids total phenolics in leaves of mulberry were measured quantitatively to be 26.41-31.28mg rutin equivalent/g and 17.20 - 22.38 mg gallic acid complement per gram, respectively.

Mulberry leaves are high in macro-and micronutrients, as well as organic acids. The leaves are high in protein in general. Mulberry leaves have a substantially greater protein content than other green leafy vegetables. Mulberry leaves are also high in ascorbic acid and minerals. The most abundant elements are calcium and potassium, with sodium being less abundant. Antinutritional

components such as cyanide, fiber, and tannin were also discovered in mulberry leaves. Mulberry root bark may operate as an effective hypocholesterolemic supplement and powerful antioxidant in hypercholesterolemic mice by inhibiting LDL atherogenic alterations and lipid peroxide generation. Mulberry stem bark extracts demonstrated the strongest inhibitory efficacy against lipid peroxidation.

As a result, metabolic disorders lipid peroxidation, such as arteriosclerosis, cholesterol, and hyperlipidemia, are likely to be inhibited. In LDL receptor-deficient mice, the effects of their main flavanol, quercetin, glycoside, affect the occurrence of atherosclerotic plaques, and the oxidative sensitivity of plasma LDL was investigated. The primary flavonoids identified in previous investigations The compounds isoquercitrin and astragalin were found in mulberry leaves. Quercetin, a flavonoid from the flavanol family. In vitro, flavonoids were found to have a considerable inhibitory effect on human LDL oxidative change (20). A variety of processes have been related to the lipid-lowering effects of mulberry leaves, including phenolics, flavonoids, and DNJ (6).

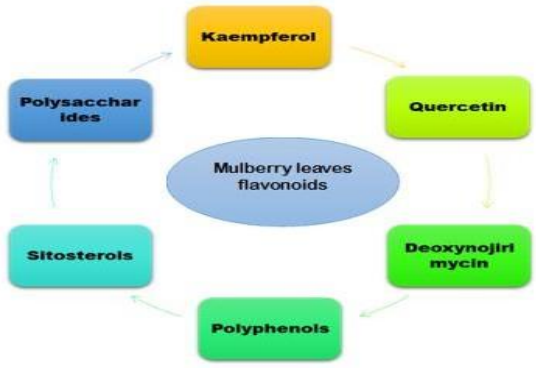

Figure 1: Phytochemicals of Mulberry Leaves

Quercetin

Quercetin derivatives also had antioxidant properties, which could help to boost lower plasma lipid levels, hepatic lipid metabolism, and minimize fat formation in adipose tissue and the liver.

Hepatic lipid metabolism can be influenced by quercetin derivatives that can help prevent obesity caused by an HFD. However, short-term feeding without obesity and the effects of derivatives of quercetin that have been studied in investigations based on obesity-related long-term feeding experiments were unclear. Mulberry leaves are high in kaempferol and quercetin, flavonoids. In humans, flavonoids, particularly quercetin, are inversely associated with total and LDL cholesterol levels. As a result, Mulberry leaves containing flavonoids are thought to have antihyperlipidemic characteristics similar to red wine. In rabbits, Rats fed an HFD were given a enriched flavonoids extract of mulberry leaves reported to lower cholesterol points. The physiological mechanisms underlying this action, however, remain unknown. We previously established that mulberry supplementation reduces cholesterol metabolism and steroid production while increasing the signaling route for peroxisome proliferator-activated receptors (Varghese & Thomas, 2019).

Furthermore, PPAR agonists have been shown to inhibit cholesterol production. As a result, we hypothesized that the mulberry leaf contains PPAR agonists, which activate the PPAR signaling system and reduce cholesterol levels in hypercholesterolemia. To explore the processes underlying the extract's hypocholesterolemic effects, Researchers examined gene expression in hypercholesterolemic mice's livers after treatment with mulberry leaf extract in polyphenols using DNA microarray analysis (38).

Deoxynojirimycin (DNJ)

One of the most effective inhibitors of alpha-glucosidase on the market is DNJ. These inhibitors reduce plasma glucose levels, resulting in reduced fatty acid input into the liver from lower triglyceride, adipose tissue, cholesterol levels. Various research has looked at the impact of Endogenous cholesterol control by flavonoids in mulberry leaves synthesis as well as flavonoids' antiatherosclerotic properties (11;18). Furthermore, Quercetin and narigin, are flavonoid chemicals are examples that have been shown to block hydroxy-3-methylglutaryl CoA reductase; the mechanism is the same as that of statin lipid-lowering drugs. Another option is that the Mulberry leaves contain water-soluble fiber that binds to bile acid and is eliminated in the feces,

reducing dietary cholesterol absorption and lowering plasma and hepatic cholesterol. Furthermore, the ileum digested this water-soluble fiber, producing Propionic and butyric acid, for example, short-chain fatty acids that can help decrease cholesterol levels. Cholesterol, Triglycerides, and low-density lipoprotein all fell dramatically in the blood circulation of rats given mulberry leaves, while high-density lipoprotein cholesterol increased (12;36).

Mulberry leaves lowered cholesterol accumulation in the liver as well as blood lipid levels. In the treatment group, in comparison, the size and number of lipid droplets in contrast to the sampler batch in hepatocytes were significantly reduced (10;20).

Phenolics, DNJ, and flavonoids were linked to the fat reduction actions of mulberry leaves by several pathways in vitro and in vivo investigations. Proliferator-activated receptor and activated protein kinase expression were raised by a mulberry leaf extract high in DNJ, quercetin, and kaempferol, resulting in an increase lipid breakdown and free fatty acid oxidation.

According to the researchers, an extract of mulberry leaves enriched with polyphenols with quercetin caffeic acid, and hydroxyflavin reduced the lipid breakdown mechanism by modulating fatty acid synthase activities, LXR regulatory element-binding proteins, and glycerol-3-phosphate acyltransferase (5).

Antioxidants

Leaves of mulberry were put through a series of tests to see if they could minimize the formation of free radicals and oxidative stress-induced damage. Extract of mulberry leaves has antioxidant activities against 1,1-diphenyl-2-picrylhydrazyl and 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulphonic acid) ranging from 1.89–2.12 dried leaves per gram equal to Trolox (8) (19). In all of the experiments, mulberry leaves were found to have an antioxidant. It has a dose-dependent impact. However, it had a weaker effect than butylated hydroxytoluene and ascorbic acid, which were previously employed as positive controls. Furthermore, the activity of rats with diabetes given extract, antioxidative defense system enzymes such as glutathione peroxidase, glutathione superoxide dismutase and glutathione-S-transferase were significantly increased. Antioxidants such as flavonoids and phenolics have been identified. A recent study found that mulberry leaf

extract fractions with higher levels of phenolic and flavonoid components have improved antioxidative activity. It may be related to the fact that potency of antioxidant and effectiveness are closely linked. For total phenolics, Pearson correlations (r) with DPPH and ABTS_ methods were 0.973 and 0.537, respectively. When compared to chlorogenic acid exhibited the powerful antioxidant impact (23).

Polyphenols

Glycosylated quercetins and kaempferols were found in mulberry leaves. There were no statistically significant variations between clones in total flavonol derivative concentrations. Mulberry leaves have ten times the amount of flavonols as mulberry fruits.

Mechanism of Action

Mulberry leaves have been linked to the regulation of PPARg target genes implicated in lipid metabolism and lipoprotein. The liver's metabolism is based on its potential to lower triglyceride and total cholesterol levels in the blood, is similar to PPARg's activity. Mulberry leaves contain alkaloid chemicals such as DNJ, which is the most powerful inhibitor of alpha-glucosidase. The inhibitors lower triglyceride and cholesterol levels by lowering plasma glucose levels and reducing fatty acid intake into the liver from adipose tissue (22). The leaves of a mulberry extract enriched with flavonoids on endogenous cholesterol production have been studied in a number of studies, as well as flavonoids' antiatherosclerotic properties (17). Furthermore, flavonoid compounds have the ability to block hydroxy-3-methylglutaryl CoA reductases such as Quercetin and narigin. Another option is leaves of mulberry contain water-soluble fiber that binds to acids of bile and is eliminated in the faces, resulting in reduced dietary cholesterol absorption and lower plasma and hepatic cholesterol. Furthermore, the ileum processesd this water-soluble fiber, releasing butyric acid and propionic acid like short chain fatty acids which can help lower lipid levels (Bhooshan & Prabhakaraiah, 2019). Plant material containing carotenoids, vitamin C, E, A polyphenols, and phytonutrients, such as mulberry leaves, raises in human blood and tissues the antioxidants status, and these components can influence LDL oxidation through a variety of mechanisms. According

to current studies, vitamin C is more effective than vitamin E at preventing LDL oxidation. Vitamin-like tocopherol and ascorbic acid level of plasma were found to be greater in Europeans who had a lower risk of cardiovascular disease. Natural carotene supplementation, according to Levy et al., lowered the risk of developing atherosclerosis in diabetics through moderating increased LDL cholesterol oxidation. Mulberry leaves contain the most carotene, so it's reasonable to assume that they lower LDL cholesterol oxidation and hence protect against atherosclerosis. Mulberry leaves have been shown to protect against atherosclerosis. The synthesis of TBARS and conjugated dienes was suppressed by quercetin, a mulberry leaf aglycone of isoquercitrin that inhibited human LDLs and copper-induced oxidative modification of rabbit. (MLBE) that stands for mulberry leaf butanol extract and isoquercitrin prevented LDL oxidation, suggesting that mulberry leaves may have this ability.

According to these findings, mulberry leaves, which contain multiple important antioxidants, antidiabetic components, and phytonutrients, effectively In STZ-diabetic rats, significantly relieved lipid abnormalities associated with diabetes and controlled blood glucose in diabetic rats. The combined action of these medicines protected diabetic mice from lipid problems. More pharmacological and biochemical research is being done to better understand the mechanism of *Morus indica* leaves hypolipidemic action (5).

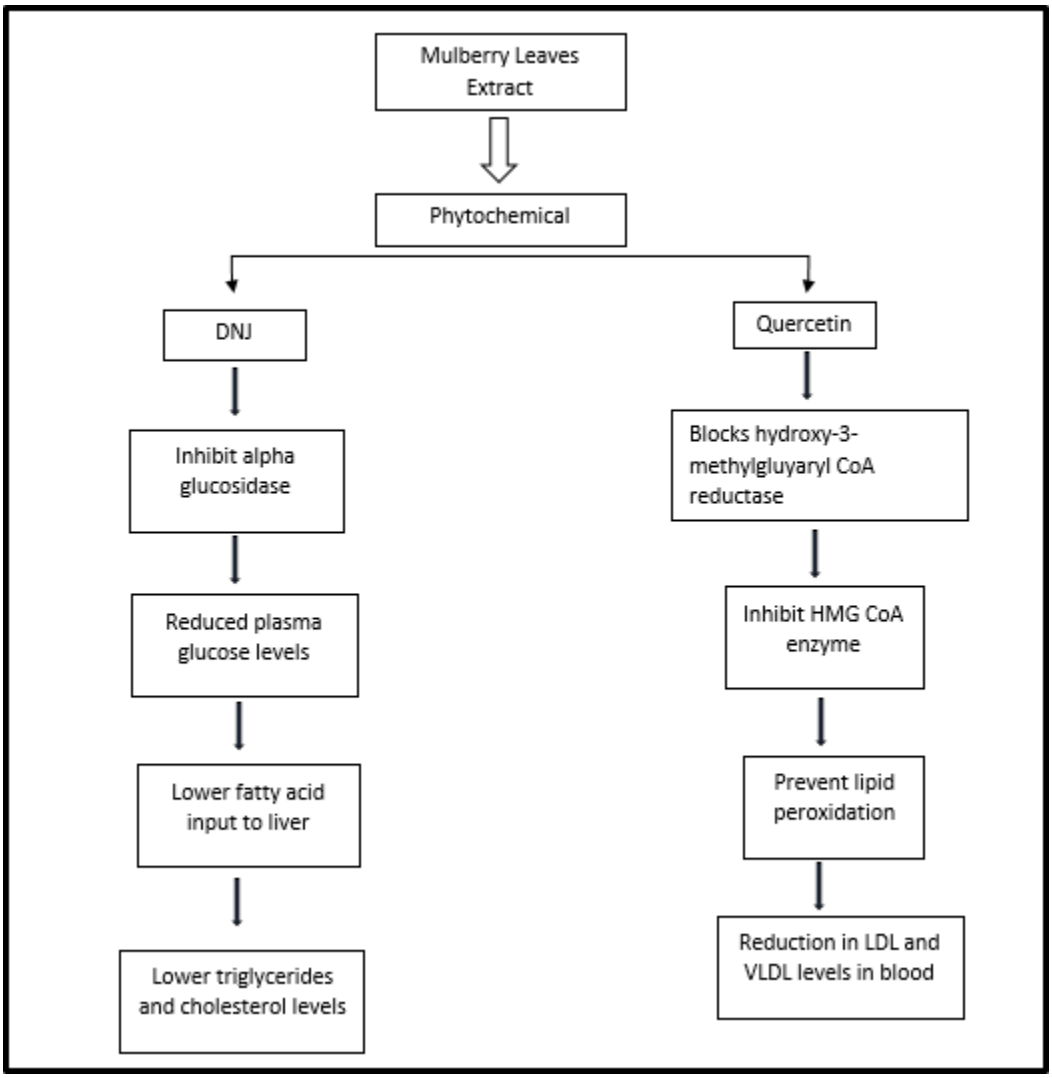

Figure 2: Mechanism of Phytochemical in Mulberry Leaves In Reducing Lipid Levels

Beneficial Effect in Hyperlipidemia

Hyperlipidemia is affected LDL, total cholesterol, and triglycerides all fell dramatically in the blood circulation of rats given mulberry leaves, whereas high-density lipoprotein cholesterol increased (5). Mulberry leaves reduced both hepatic cholesterol buildup and blood lipid levels. In

the treatment group, in hepatocytes, the digit and area of fat globule were considerably smaller sampler group. Flavonoids and phenolics were connected to the fat-reducing advantages of leaves of mulberry by a multitude of routes in both in vitro and in vitro investigations (34). By modulating the activities of fatty acid synthase, sterol regulatory element-binding proteins, glycerol-3-phosphate acyltransferase, and liver X receptor, polyphenol-rich mulberry leaf extract contains hydroxyflavin, quercetin, and caffeic suppressed formation of fatty acids. (5). Mulberry leaves were used to safeguard cardiac architecture and function in a variety of experimental animals. The results demonstrated that providing mulberry leaves to rats on a daily basis prevented isoproterenol-induced cardiac injury in rats (ISO). In comparison Compared In comparison to the sampler batch, The therapy batch had fewer elevated myonecrosis regions, smaller myocarditis, and elevated cardiac markers. Mulberry leaf therapy was connected to a near-normal structure of cardiac tissues in myosin-induced myocarditis rats, with reduced inflammatory cytokines and fibrous forms infiltrated. In the trial, the therapy was protected by reversing cardiac hemodynamic function myocardial diastolic and systolic dysfunction, demonstrating a protective effect against left ventricular remodeling (1).

Mulberry leaves have been studied in a variety of ways for their anti-hyperlipidaemic effects. Supplementing with tablets made with leaves of mulberry contains 0.357 mg of the supplement of DNJ lowered LDL-C (5.7 percent, $p<0.5$), TC (4.8 percent, $p<0.5$), and TG (15.1 percent, $p<0.5$) and elevated HDL-C (18.7%, $p<0.5$) in patients with early-stage dyslipidemia in a 12-week single group research. According to one study, mulberry leaves were found to be more effective at lowering cholesterol than simply changing one's lifestyle (32). Another 12-week single-group study looked into the potency of tablets of mulberry leaves per day containing 35mg of DNJ in hypertriglyceridemia sufferers.

The therapy had a significant effect on triglycerides, which reduced from 310 80 mg/dL at standard to 242 76 mg/dL at 12 weeks, but no other lipids changed statistically significantly (29). Mulberry leaves can also be made into tea. After an 8-week intervention period, daily administration of 6 g mulberry leaves tea lowered TG (15.9 percent), TC (9.7%), and LDL-C (2.01 percent) in case with

increased TG, TC and LDL-C. Whenever contrast upto standard range however, statistical differences between the groups were discovered at the end of the trial.

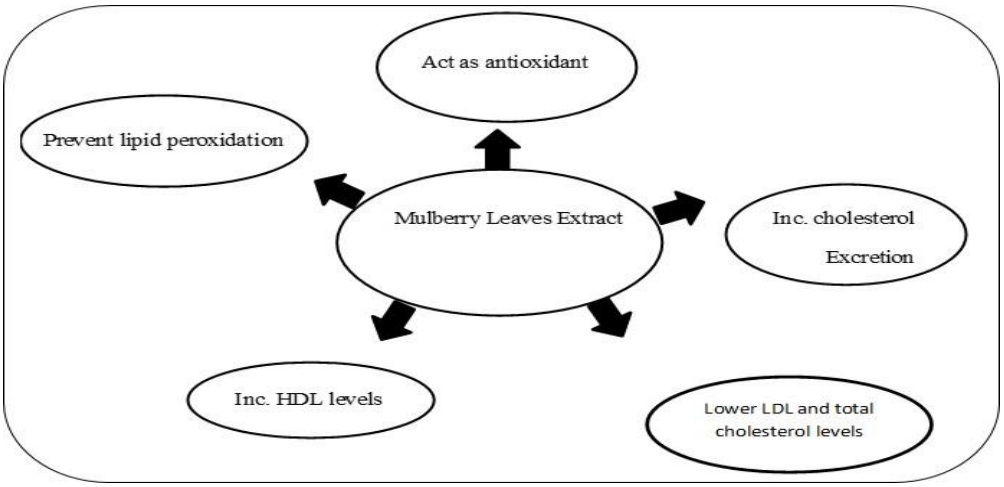

Figure 3: Physiological Benefits of Mulberry Leaves Extract

Animal trials (rat study)

Hassan et al., 2020 (9) conducted a study to observe the effect of mulberry leaves on experimental hyperlipidemic rats. The Ethics Committee of Zhejiang Chinese Medical University approved this experiment, which took place in a Chinese animal laboratory (Hangzhou, China). For five weeks, high-fat diet and ML were given to rats. To investigate how ML influenced hypercholesterolemia, researchers looked at total cholesterol (TC), blood lipid levels, and total bile acid in the liver and faeces (9). The degenerative alterations and fat accumulation in the liver were visualized using Oil red O staining and Harris's hematoxylin staining proliferator-activated receptor, ATP binding cassette transporter G5/G8 protein expression, cholesterol 7 hydroxylase 1 protein expression, nuclear transcription, and factor farnesoid X receptor, was measured using an immunohistochemical assay, and protein expression scavenger receptor and LDL receptor class B

type I was measured using western blotting. The findings revealed that ML therapy reduced hepatocyte lipid degeneration by LDL cholesterol levels, lowering blood TC and as well as TBA and TC contents of liver; raising levels of HDL-C serum, as well as TBA and fecal TC contents; and reducing degeneration of lipid hepatocyte. PPAR, Hepatic LDL R, and FXR protein expression were all reduced by ML therapy, but CYP7A1 protein expression was increased, and the ABCG5/ABCG8 ratio remained steady. The findings show that ML increases TBA and cholesterol oxidation via FXR and CYP7A1-mediated pathways suggesting that regulation of RCT could be one of techniques of ML's anti-hypercholesterolemia.

Trimarco et al., 2015 conducted research to examine Insulin Sensitivity, Endothelial Function and Lipid Profile in Dyslipidemias: Effects of a Nutraceutical Combination with Mulberry; the Ethnic Committee approved the Federico II University of Naples' study protocol, with the Helsinki Declaration's requirements. For two weeks, dietary advice was given to sufferer and a no real treatment. Division of patients was done into one of 2 batches following run-in phase: (1) Combination A for four weeks, and then Combination B for four weeks (Monakolin K 3.3 mg, Red yeast rice), Astaxanthin, Berberine 500 mg, Folic Acid, and Coenzyme Q10]; (2) Combination B for four weeks. Mixture B lowered by 120 mg/dl in 55.5 percent of LDL cholesterol in patients, while mixture A only lowered LDL cholesterol lowered 130 mg/dl in 21.7 percent of patients (p 0.027). Total cholesterol, Triglycerides, HDL and LDL cholesterol were all lowered in all of the regimens ($p<0.003$). Mixture B individuals had decreased total and LDL cholesterol levels (p 0.005). Mixture B decreased fasting glucose, insulin, the HOMA index and plasma levels of glycated haemoglobin ($p<0.005$). By increasing the amount of Monacolin K and Berberin in the NUT Combination and adding extract of morus alba glucose metabolism and plasma cholesterol levels are improved. These effects may result in a greater improvement in cardiovascular prognosis (33).

Kobayashi et al., 2015 (14) conducted research at Japan's Osaka Institute of Technology; the extract of mulberry leaves effect on Cholesterol Synthesis in Hypercholesterolemic Mice were investigated in this study. When mulberry leaf extract-treated mice were compared to control

group animals, LDL,TC, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase and TC levels were all reduced in liver. In addition, the mulberry extract increased innate and acquired immunity in eosinophils, macrophages, killer cells, B cells, neutrophils, and T cells, among other lymphocytes, by triggering scavenger and Toll-like receptors and activating pathways. The data suggest that mulberry leaf quercetin and kaempferol activate PPAR signaling pathways via activating PPAR, Pparg genes and PPAR, transcription of Ppara, and activation of signaling pathways of PPAR. Cholesterol production and immunostimulation are both reduced as a result of these processes (14).

Sun et al (28)., a study was conducted in 2015 at Japan's Shimane University School of Medicine. In LDL receptor-deficient mice, the impact of mulberry leaves and its primary quercetin flavonol glycoside on the formation of atherosclerotic plaques and low density lipoproteins susceptibility of alteration of oxidative stress were noticed. Male mice were divided into four groups at random. The sampler batch were given 2g cholesterol with atherogenic diet and with 18mg/100 g cocoa butter. For the Q3MG, mulberry groups and quercetin the same atherogenic diet was supplemented with 0.005 g Q3MG per 100 gram, 0.005 g quercetin per 100 gram, and 4 gram powder of mulberry leaves in dried form respectively. The mice were offered a variety of diets over eight weeks. When compared to control rats, the sensitivity of oxidative alteration to LDL was considerably reduced in mulberry-treated mice and Q3MG-, as proof by a 42.1 and 41.3 percent lengthening of conjugated diene production in lag phase, respectively. In both mulberry-treated mice and Q3MG-, the atherosclerotic lesion area was considerably reduced by 52 percent when compared to controls. On the other hand, the quercetin group demonstrated no protection against LDL oxidation or the formation of atherosclerotic plaques. Finally, Mulberry leaves enhanced LDL resistance to oxidative modification, slowing atherosclerosis progression in LDLR/ mice. These antiatherogenic and antioxidative properties were predominantly attributed to Q3MG, the most abundant in mulberry leaves is flavonol glycoside (28).

Lim et al (16)., 2020 performed a study at Dong-eui University of science and technology, Korea, to examine the Protective. He employed a mixture of yacon extract and mulberry leaves extract

and to induce in rats with hyperlipidemia because, since the treatment of atherosclerosis has become a social problem, more researches were conducted to see the effect of herbal products on hyperlipidemia. All the groups of rats were habituated to the sustain setting for 6 days before being given for four weeks the high fat diet until their poundage exceeded 30% of the usual range. To see how mulberry leaf was affected hyperlipidemia in Sprague-Dawley rats, 1 percent, 3 percent, and 5 percent of MLYT were given to the rats. The high-fat diet group (G2) had a 26.2 percent rise in aspartate transaminase (AST) compared to the regular diet group (G1) ($P<0.05$). However, when compared to G2, AST was significantly lower in the HFD with hydroxycitric acid (0.5%) diet group no.3 and the MLYT treatment batches. The MLYT-treated groups showed substantial improvements in LDL, total cholesterol, triglycerides, and phospholipids (P0.05). The lipid content of the liver and feaces aided these changes in the liver and feces. In rats, MLYT significantly reduced the level of lipid peroxidation produced by an HFD. HMG-CoA reductase activity is measured in 3-hydroxy-3-methylglutaryl-coenzyme.The results indicated that mixture of mulberry and yacon had beneficial effect towards hyperlipidemia (16).

Sukandar et al. 2016 (27) conducted research at the Institute Teknologi Bandung's School of Pharmacy in Bandung, Indonesia. To test their antihyperlipidemic effects, Binahong leaves, and Mulberry leaf extracts were mixed. Division of rats were done into 7 batches simvastatin 3.6 mg/kg BW, binahong leaves extract 100 mg/kg and mulberry 100 mg/kg, binahong extract 100 mg/kg BW and mulberry 200 mg/kg BW, mulberry leaves extract 200 mg/kg for 30 days, rats were fed an orally administered high-fat diet containing cholic acid (0.25 percent of chow), and propylthiouracil (10mg/kg BW) cholesterol (210 mg/kg). Following that, all groups were given the tested substances for the next 14 days, with the exception of the control group. T0 (immediately after induction), T7 (seven days later), and T14 lipid profiles were assessed. At T14, differences is observed by the M210, B60+M110, and B110+M210 batches and the control group, with values of 32.68 percent, 35.39 percent, and 45.81 percent (in total cholesterol reduction) and 37.86 percent, 38.16 percent, and 47.99 percent, respectively, contrast to the sampler batches (in reduction of triglyceride). At day 14, the M210, B60+M110, and B110+M210 groups significantly

lowered TG and TC levels. Both extracts combined have much higher Binahong, and mulberry extracts both have reduced lipid action (27).

Li et al. 2020 (15) conducted a study to observe the antihyperlipidemic effect of Mulberry. The study was carried out in China. Hyperlipidemia is a global disease with a clear gender divide in prevalence. However, it is unknown how gut bacteria influence hyperlipidemia progression. In this study, we discovered that mulberry leaf extract reduced hypertriglyceridemia and hyperglycemia in female and male mice with similar potency. However, female mice had a more substantial effect on hypercholesterolemia. Further research revealed that DNJ suppressed the lipogenic genes, particularly cholesterol biosynthesis genes, in a sex-specific manner. According to a metatranscriptomic study, oral treatment of DNJ caused a more substantial alteration in female then in mice of male specie gut microbiota. In a sexually dimorphic way, DNJ increased the formation 3-indolepropionic acid by enriching Ackermann's and Clostridium group XIVa bacteria (IPA). Importantly, IPA was found to be intimately linked to DNJ's antihyperlipidemic activity and to have a In vitro and in vivo, it has a strong lipid-lowering impact. Our studies accepted a procedure through that deoxynojirimycin improves sex-specific hyperlipidemia, providing a detailed theoretical underpinning for the therapeutic application of DNJ as a sex-specific antihyperlipidemic agent (15).

Tenda PE et al., 2021 (30) conducted a study in Nusaputera College of Pharmacy; fresh leaves of mulberry, that is considered as therapeutic herbs consumed by individuals to reduce lipid profile, were studied in Semarang Central Java, Indonesia. According to a recent study, mulberry leaves include flavonoids, which lower cholesterol, and tannins, which prevent food, particularly fat, from being absorbed in the GI tract. The researchers want to see how mulberry leaf ethanol extract impacts HDL levels and foam cell growth. An atherogenic diet was fed to male Wistar strain rats. Thirty male rats were split into six groups: control, negative control, +sample control, and 3 ranges of mulberry leaf extract (25, 50, and 100 mg/200g BW rats). On days 0, 28, 35, and 42, HDL levels were evaluated before and after therapy. A range of 110 mg/200 g body weight, the ethanol extract was found to be the most effective dose for increasing HDL while also reducing the formation of

aorta wall foam cells. Finally, the ethanolic ML extract have the ability to be used as natural cholesterol-lowering agent (30).

Table 3: Therapeutic Benefits of Mulberry Leaves Extract

Therapeutic Potential	Author, Year	Sample	Method	Results	Reference
Cholesterol-lowering Effect	Tenda et al., 2021	30 Wistar strain rats	Thirty male rats were split into six groups: control, negative control, positive control, and three doses of mulberry leaf extract were given.	Dosage of 100 mg/200 g BW, the extract made with ethanol was concluded to be the most potent dosage for increasing HDL while also reducing the formation of aorta wall foam cells.	(Tenda& Toyo, 2021)
Anti-Hyperlipidemic Effect	Yougui Li et al., 2020	35 experimental Rats	Both male and female mice fed with extract of mulberry leaves with dosage of 200mg BW.	Studies accepted the procedure through that deoxynojirimycin enhance gender-specific hyperlipidemia.	(Li *et al.*, 2020)
Anti-Hyperlipidemic Effect	Sukandar et al., 2016	30 male rats	The rats were divided into 7 groups,simvastatin 3.6 mg/kg BW, binahong leaves extract 100 mg/kg and mulberry 100 mg/kg , binahong extract 100 mg/kg BW and mulberry 200 mg/kg BW,	At day 14, the groups significantly lowered TG and TC levels. Both extracts combined have much higher Binahong, and mulberry extracts both have reduced lipid levels.	(Sukandar *et al.*, 2016)

			mulberry leaves extract 200 mg/kg.		
Cholesterol-lowering Effect	Lim et al., 2020	60 experimental rats	To see how mulberry leaf was affected hyperlipidemia in Sprague-Dawley rats, 1 percent, 3 percent, and 5 percent of MLYT were given to the rats.	The results indicated that mixture of mulberry and yacon extracts had beneficial effect towards hyperlipidemia..	(Lim *et al.*, 2020)
Anti-Hyperlipidemic Effect	Jiang et al., 2017	48 male Sprague rats.	For five weeks, rats were fed a high-fat diet and given ML.ML powder was suspended in pure water according to dosage with final concentrations as 0.09, 0.06, and 0.03 g/ml prior to intragastric administration.	The findings revealed that ML reduced hepatocyte lipid degeneration by LDL cholesterol levels, lowering blood TC and as well as liver TC and reducing hepatocyte lipid degeneration.	(Jiang *et al.*, 2017)
Cholesterol-lowering Effect	Kobayashi et al., 2015	35 male rats	To find the result, we have given a high-fat diet and mulberry extract rich with polyphenols containing essential flavonoids for four weeks.	The data suggest that mulberry leaf flavonoids activate PPAR signaling pathways via activating PPAR and PPAR, transcription of Ppara and Pparg genes, and	(Kobayashi *et al.*, 2015)

				Cholesterol production and immunostimulation are both reduced as a result of these processes.	

Conclusion

This review spotlights the therapeutic activity of mulberry leaves in healthcare. Leaves of mulberry can be a favorable choice for regulating chances related to heart diseases. A number of important phytochemicals were identified in mulberry leaves that can be proven beneficial for maintaining good health and helpful in the treatment of various diseases. The mulberry leaves were used to treat coughs, fevers, hyperlipidemia, hypertension, and hyperglycemia in traditional medicine for a long time. It has been observed for decades that plants are potential source of several bioactive compounds. It is proven in previous studies that mulberry leaves are safe to use and possesses medicinal properties. This research is supposed to be helpful in future research and will reduce the burden of disease after clinical trials and experiments. Therefore, the present study will contribute evidence-based results regarding the antihyperlipidemic effects of mulberry leaves. The mulberry leaves have significant antihyperlipidemic effects; therefore, consumption of these leaves can reduce the burden of morbidity and mortality.

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