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EVALUATING THE CARDIOMETABOLIC IMPACT OF MULBERRY INTAKE: A META-ANALYTICAL PERSPECTIVE

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ABSTRACT

The study aimed to thoroughly assess how eating mulberries affects heart and metabolic health in adults. Cardiovascular and metabolic risk factors, which are well-established predictors of chronic disease, stand as the foremost causes of mortality worldwide. This syndrome causes changes in the blood, including difficulty processing glucose, elevated levels of insulin, resistance to insulin, increased triglycerides, decreased levels of HDL cholesterol and higher amounts of small, dense LDL cholesterol. These changes in the body also cause inflammation, shown by increased C-reactive protein and other markers. High blood pressure, particularly systolic blood pressure, is a significant risk factor for CVD and accounts for over half of stroke and ischemia deaths. Many medicinal plants are used as natural remedies for diseases. One such plant is mulberry, which is rich in nutrients and bioactive compounds. There are different types of mulberries, including white, black, and red mulberries. They grow in many parts of the world, both wild and cultivated and offer various health benefits. One such compound found in mulberry leaves is 1-deoxynojirimycin (DNJ), which helps block an enzyme called α-glucosidase. This action prevents the breakdown of certain sugars in the body, which can be helpful in managing conditions like insulin resistance and glucose problems, which are linked to cardiovascular disease risk. Mulberries contain phenolic compounds like flavonoids and anthocyanin's, known for their antioxidant properties. These compounds are believed to help prevent certain risk factors of cardiovascular disease (CVD) and may even have immune-boosting and anti-cancer effects. Mulberry leaf extract changed how certain genes and proteins related to glucose balance work in liver cells. Mulberry leaf extract boosted certain pathways in the body and increased the movement of glucose transporter-4 (GLUT-4) in muscles and fat tissues. Animals given mulberry leaves also saw significant drops in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and triglycerides (TG), along with a rise in high-density lipoprotein cholesterol (HDL-C) in their blood. Eating mulberry leaves stopped the increase in body weight caused by a high-fat diet. Mulberry leaves also reduced the number of fat cells and the size of fat droplets in those cells.

KEYWORDS

Mulberries, Cardiovascular effects, Metabolic disorders, Randomized controlled trials, DNJ biosynthesis, Alkaloids and Flavonoids.

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INTRODUCTION

[1]A recent review found that adding mulberry to your diet could help improve several factors that affect heart and metabolic health.

Several interventional studies have investigated the potential health-promoting effects of mulberry consumption on cardio metabolic risk factors.

While some randomized controlled trials (RCTs) have demonstrated positive impacts of mulberry on cardiovascular risk factors.

Mulberry (Morus alba), from the Moraceae family, is rich in antioxidant phenolic compounds like flavonoids and anthocyanin's, which may reduce cardiovascular disease (CVD) risk factors and offer immunomodulatory and antitumor benefits.

[2]Mulberry is a versatile plant rich in nutrients and phytochemicals, making it a valuable functional food. Its fresh fruits are used in food production, such as juice, jam, and jelly, while the leaves are crucial for silkworm feeding and are also used as dairy animal feed to enhance milk production. In Asia, mulberry leaf tea is popular for its health benefits. Traditionally, various parts of the mulberry tree, including root bark, leaves, and fruits, have been used to treat fever, cough, hyperlipidemia, hypertension, and hyperglycemia. Today, mulberry leaf products, available as powders, extracts, and capsules, are marketed as dietary supplements for weight and blood glucose control.

[3]The primary reason mulberries are grown is because their foliage is the only food source for the silkworm Bombyx mori L. Drawn in by its significant biological role, the polyhydroxylated piperidine alkaloid 1-DNJ is the primary active ingredient in mulberry plants. Nonetheless, the mulberry's naturally occurring alkaloid DNJ content gains significance due to its application in numerous domains. It naturally occurs in certain microbiological strains, plants, and insects as a secondary metabolite product. However, DNJ content in plants and insects is rather low.

1-Deoxynojirimycin (DNJ) is a chemical with a wide range of applications that is anti-aging, anti-inflammatory, antioxidant and anti-diabetic.

Weather and other characteristics of the host plants growth zones, such as Mulberry types, geographic locations, soil characteristics, meteorological factors, and harvesting time, have a significant impact on DNJ biosynthesis.

DNJ Diabetes Application

The result of a complicated metabolic illness, diabetes mellitus is characterized by elevated blood glucose levels and abnormalities in insulin secretion. It is linked to an increased risk of cardiovascular disease. For many years, mulberry leaves have been used as a natural remedy for the treatment of diabetes since extracts from them have demonstrated verified antidiabetic properties in experimental animals. Disaccharides cannot be absorbed or digested; instead, they pass through the colon and are finally eliminated in humans when given DNJ because it inhibits the α-glucosidase activity that impacts the conversion of disaccharides to monosaccharides. Thus, it lowers blood sugar levels and decreases the absorption of glucose.

Chemical composition

[4]Chemical analysis of mulberry leaves reveals ash content between 8.19–12.63% and moisture content between 72.16-79.35%. These leaves are a valuable source of macro and micronutrients, organic acids, and are notably rich in protein, surpassing other green leafy vegetables. They also contain ascorbic acid, calcium, and potassium, with sodium present in smaller amounts. Additionally, mulberry leaves contain antinutritional components such as fiber (8.74-13.70%), cyanide (1.01-2.14mg/kg) and tannin (3.54-5.32mg/kg). Mulberry leaves contain iminosugar alkaloids, mainly 1-deoxynojirimycin (DNJ). DNJ concentrations in dried leaves vary from 0.1341–3.483 mg/g across different varieties.

The leaves also have several antioxidative compounds, including phenolic acids (caffeic, Gallic, protocatechuic, p-hydroxybenzoic, vanillic, chlorogenic, syringic, p-coumaric, ferulic, and m-coumaric acids) and flavonols (rutin, isoquercitrin, and astragalin). Total phenolics range from 16.21-24.37mg gallic acid equivalent/g, and total flavonoids range from 26.41- 31.28mg rutin equivalent/g.

[5]Improving lifestyle is key to preventing cardiovascular disease, and diet is one of the most effective ways to lower and control blood pressure (BP). In recent decades, researchers have emphasized low-salt diets as a highly effective method for reducing bp.

[6]Dietary changes are essential for treating high blood pressure (arterial hypertension). American and European guidelines recommend eating more fruits, vegetables, whole grains, and low-fat dairy products, while reducing red meat, sugar and trans fats. Caloric restriction can lower blood pressure in people who are normotensive, prehypertensive and hypertensive. Nutrition is now seen as an important aspect of medicine, including cardiology. Studies comparing blood pressure among different groups-raw food vegans with a sedentary lifestyle, endurance athletes on a Western diet and sedentary individuals on a Western diet-found that blood pressure was significantly lower in the vegan group.

RAW MATERIALS OF MULBERRY

[7]Mulberry fruit (Morus alba var. Chiang Mai) was sourced from Kamnulchul Farming in Thailand. Fully ripe fruits were freeze-dried to make mulberry fruit powder (MFP) and stored in vacuum-sealed aluminum foil bags at -20°C. Other ingredients used to make the jelly included carrageenan, locust bean gum, konjac, sucralose and citric acid.

NUTRITIVE VALUE OF MULBERRY

We measured the amount of water, ash, protein, fat, carbohydrates and both insoluble and soluble fiber, as well as sugar using a standard method called AOAC. Then, we calculated the number of calories using the levels of protein, fat, and carbohydrates.

[8]Dietary fiber is made up of plant parts that our stomach and small intestine can't digest, including structural and storage polysaccharides and lignin. The American Dietetic Association recommends that people should eat enough dietary fiber from various plant foods. Healthy adults should aim for 20-35 grams of fiber daily, while children should have their age plus 5 grams each day. However, most people don't meet these recommendations because they don't eat enough fiber-rich foods like fruits, vegetables, whole grains and legumes.

[9]In traditional Chinese medicine, mulberry leaves are used for treating inflammation, colds, and viral infections. Recent studies show that mulberry leaves also have strong anti-diabetic effects. Some of the main ways mulberry leaves help with diabetes include blocking alpha glucosidase activity in the intestine, managing lipid metabolism, protecting pancreatic cells, reducing insulin resistance, increasing glucose uptake by tissues, and improving oxidative stress levels. These actions help regulate blood sugar levels effectively.

[1]cardiometabolic risk factors are leading causes of death worldwide, responsible for over 18.6 million deaths in 2019. These factors cause significant blood changes, including glucose intolerance, high insulin levels, insulin resistance, high triglycerides, low HDL, and increased small dense LDL, leading to inflammation marked by elevated CRP and other inflammatory markers. Obesity, indicated by increased weight, BMI, waist circumference, and central fat, results from metabolic syndrome and contributes to cardiovascular disease (CVD). High systolic blood pressure is also a major risk factor for CVD and related deaths, accounting for over half of stroke and ischemia fatalities. Managing these risk factors has increased medical costs and lost productivity. Recently, there has been a rise in the use of herbal supplements and medications to control cardiometabolic risk factors.

[10]A lifestyle that is unhealthy is linked to a number of health issues. One of them is being overweight or obese, which is defined as having a body mass index (BMI) of 30 or higher. Another ailment that can damage arteries and increase the risk of developing cardiovascular disease is excessive blood pressure, sometimes known as hypertension.

Hyperglycemia, or high blood sugar, is a condition when the body cannot use or make insulin properly. It can also result in problems like renal disease, eyesight loss, and cardiovascular disease. High blood cholesterol, especially LDL cholesterol, or hyperlipidemia, can lead to artery plaque formation, which increases the risk of cardiovascular disease and stroke. Last but not least, insulin resistance is the result of cells that no longer use insulin as intended, which raises blood sugar levels and ultimately causes type 2 diabetes. It is frequently linked to both physical inactivity and obesity.

Because of their possible health benefits, particularly the ability to control blood sugar levels, mulberries have long been utilised in Chinese medicine. According to recent studies, mulberries may help with cardiometabolic risk factors include blood pressure, lipid profile, and fasting blood glucose levels.

Additionally, mulberry extract has been demonstrated to help lower fasting blood sugar levels and HbA1c in individuals with type 2 diabetes, according to a meta-analysis of randomised controlled trials. Furthermore, randomised, double-blind, placebo-controlled trials have shown that mulberry fruit extract improves skin elasticity and reduces wrinkles in postmenopausal women as well as improves cognitive performance and lowers anxiety in healthy older individuals. Finally, mulberry leaf extract was found to enhance exercise performance and decrease muscle damage in a study conducted on young, healthy men. These findings suggest that mulberry extract may be a valuable dietary supplement for a range of illnesses.

The Importance of Mulberry

[11]Therapeutic Value of Mulberry

Since ancient times, humans have relied on plants to treat various diseases. Even with the progress in modern medicine and the pharmaceutical industry, therapeutic plants are still widely used to prevent and treat many medical conditions. As a result, many scientific laboratories focus on herbal medicine, and new plant-based drugs are being developed.

Mulberry, in particular, has been studied for its numerous health benefits. In addition to its antioxidative, anticancer, and blood sugar-lowering effects, research has confirmed that mulberry also has hypolipidemic (cholesterol-lowering), liver-protective, antibacterial, and anti-obesity properties. These benefits are linked to the bioactive compounds found in its leaves, fruits, and root bark.

[12]For effective glycemic management overall, postprandial (PP) hyperglycemia and PP glucose excursions must be minimised. There is no specific nutritional intervention that is preferred, even though the majority of therapeutic lifestyle interventions that lower calorie intake would effect this.

[13]It has been demonstrated that the non-toxic natural therapeutic mulberry (Morus indica L.) has hypoglycemic, hypotensive, and diuretic effects. The anti-diabetic efficiency of glibenclamide, the gold standard medication, was compared with the hypoglycemic effect of mulberry leaves.

Plant Part Health Benefits Biological Compounds References

[14]***Leaves***

*Health Benefit: Anti-diabetic activity

*Composition: Deoxynojirimycin, Moranolin, 2-aryl-benzofuran

*Health benefit: Anticancer activity

*Composition: Morin, Kuwanon S, 8-granilapigenin,ciclomulberrin, morusin, ciclomorusin, atalantoflavones, Kaempherol-3-O-glucoside (Astragalin) and derivates, Quercetin and derivates, Epicatechin, moracins, phenolic acids (gallic, protocatechuic, vanilinc, p-coumaric, ferulic), apigenin and derivates.

*Health Benefit: Antioxidant activity

*Composition: Quercitrin, rutin, Eriodictyol, gallic acid, chlorogenic acid, sinapic acid, Hypolipidemic effect 1-Deoxynojirimycin, Caffeic acid, Cyanidin-3-O-rutinoside

Neuroprotective activity γ-aminobutyric acid, gallic acid, chlorogenic acid.

*Health benefit: Anti-inflammatory effects

*Composition: Chlorogenic acid, Caffeic acid, Anti-viral activity Cyanidin-3-O-rutinoside, 1Deoxynojirimycin.

Fruits

*Health Benefit: Anti-diabetic activity

*Composition: Polysaccharides (FMAP, MFP, MFP-1, MFP-2, MP, PMF1, PMF2, PMF3, MFP3P, JS-MP-1)

*Health Benefit: Anticancer activity

*Composition: Vanillic acid, Caffeic acid, ferulic acidprotocatechuic acid, gallic acid

Root bark

*Health Benefit: Anti-diabetic activity

*Composition: 1-Deoxynojirimycin

*Health Benefit: Anticancer activity
*Composition: Morusin, oxyhidromorusin, moracins,Glycoside, 5, 20Dihidroxyflavone-7, 40-di-O-D-glucosides.
*Health benefits: Antioxidant activity
*Composition: Mulberroside A, Mulberoside C.
*Health Benefit: Neuroprotective and hepatoprotective activities
*Composition: Sanggenones (B, D, E, G, M, O, T)
*Health Benefit: Anti-inflammatory effects
*Composition: Mulberrofurans, Morusin, oxyhidromorusin, sanggenones.

Economic Significance of Mulberry

Mulberry is highly valued by the scientific community for its medicinal properties and plays important roles in various industries, making it a key player in the global economy. It is essential in sericulture as the sole food source for silkworms, which produce silk from B. mori. The quality of mulberry leaves directly impacts silk production. While mulberry is primarily grown for silkworms, it also serves as an excellent alternative to fodder crops for feeding domestic animals in countries like China, India, and Korea. Mulberry leaves are now used as dietary supplements to enhance animal nutrition. Studies have shown that adding mulberry leaves to dairy animal feed increases milk production and improves the milk's lipid and fat content.

Mulberry also has a significant impact on the cosmetic industry. It is an ingredient in various creams, bath gels and other products, known for its ability to reduce aging-related skin conditions and act as a skin whitening agent. Mulberry inhibits tyrosinase, an enzyme involved in melanin production, contributing to its skin-whitening effects.

Cultivation Method of Mulberry

Consumers are increasingly concerned about food quality and safety. Conventionally grown foods often contain high levels of pesticides, nitrates, heavy metals, hormones, and antibiotics, and they may lack essential nutrients and antioxidants. This has led to a growing demand for organically grown foods, which are seen as safer and healthier. Organic food production avoids synthetic fertilizers, herbicides, pesticides, and other chemicals.

Organically grown foods are becoming more popular due to their health benefits and positive nutritional impact. Additionally, organic farming supports soil health and biodiversity, promoting sustainable agriculture. However, it is often more labor-intensive and may require more land than conventional farming.

Organic mulberry farming involves growing mulberries using natural methods like crop rotation, mulching, composting, and vermicomposting. Alternative farming methods refer to types of agriculture that differ from conventional practices. These include in vitro micropropagation, vertical farming (with soil-less techniques like hydroponics, aquaponics, and aeroponics), permaculture, polyculture and biodynamic farming.

****Biological Properties and Clinical Efficacy***

Anti hyperglycaemic effect

[2]Mulberry leaves, when given as a single dose or over a long period, help improve blood sugar levels in animals. They reduce spikes in glucose after meals and bring fasting blood sugar levels, HbA1c, and insulin levels closer to normal in diabetic animals. Mulberry leaves also restore the size and number of pancreatic beta cells, which produce insulin, in diabetic animals. The most effective compound in mulberry leaves for lowering blood sugar is DNJ. DNJ blocks enzymes in the digestive system that break down carbohydrates, reducing their absorption. Mulberry leaves also affect genes and proteins involved in glucose regulation in the liver cells.

Clinical studies have shown that mulberry leaves are effective in controlling blood sugar levels. The main active component, DNJ, determines the amount of mulberry leaves consumed. The effective dose of DNJ for humans ranges from 6 to 24mg. Taking DNJ enriched mulberry leaf products helps lower blood sugar levels after meals. This effect is seen within 30 minutes of taking the supplement, regardless of the type of carbohydrates consumed. However, a higher dose of DNJ may be needed when consuming complex carbohydrates. Daily

intake of mulberry leaf capsules for 4 weeks improved long-term blood sugar control in prediabetic patients. However, mulberry leaf supplementation did not affect blood sugar levels in individuals without diabetes. Additionally, mulberry leaf powder enriched with DNJ did not change fasting blood sugar levels in healthy volunteers over a 38 day treatment period.

Anti hyperlipidaemic effect

Mulberry leaves help improve cholesterol levels in animals by reducing total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol. They also reduce fat buildup in the liver by decreasing the number and size of fat droplets in liver cells. DNJ, phenolics, and flavonoids found in mulberry leaves are responsible for these effects. They work by activating proteins like AMPK and PPAR-alpha, which increase fat breakdown and usage for energy. Mulberry leaf extracts containing compounds like quercetin and kaempferol also decrease fat production by regulating enzymes involved in fat synthesis. Drinking brewed mulberry tea daily has shown effectiveness in reducing total cholesterol, triglycerides, and LDL cholesterol levels in individuals with elevated levels after an 8-week period. It's noteworthy that mulberry leaves can also benefit those with both diabetes and dyslipidemia. Mulberry leaf products have also been found to improve lipid profiles in patients with type 2 diabetes who have abnormal lipid levels in a 4-week trial. These effects were comparable to conventional therapy with 5 mg/day of glibenclamide, although glibenclamide is primarily an antidiabetic drug and might not be the most suitable comparison for lipid-lowering effects.

Anti-obesity effect

Mulberry leaves help prevent weight gain caused by a high-fat diet. Animals fed mulberry leaves ended the study with lower body weight compared to the control group, and they also had reduced visceral fat and body fat mass. Mulberry leaves decrease the number and size of fat cells, leading to lower fat accumulation. Long-term consumption of mulberry leaves gradually increases levels of adiponectin, a hormone that fights obesity. Phenolics found in mulberry leaves are believed to be responsible for their anti-obesity effects. Mulberry leaves also reduce the expression of key enzymes involved in fat production, such as FAS and ACC, by inhibiting the formation of new fat cells.

Antihypertensive effect*

Mulberry leaves help normalize high blood pressure and heart rate in animal studies. They improve blood vessel function by restoring normal dilation and constriction responses. Mulberry leaves lower blood pressure and heart rate by inhibiting the angiotensin-converting enzyme (ACE) and acting as a calcium channel blocker, which reduces calcium entry into cells and decreases vascular contraction. The presence of γ-aminobutyric acid (GABA) in mulberry leaves may also contribute to their blood pressure-lowering effects.

Antioxidative and anti-inflammatory effects

Mulberry leaves have strong antioxidant properties, meaning they can fight against free radicals and protect tissues from oxidative damage. Studies have consistently shown that mulberry leaves can reduce oxidative stress in a dose-dependent manner. They inhibit lipid peroxidation, a process that damages cell membranes, as seen in tests measuring thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) levels. Mulberry leaves also help normalize elevated MDA levels in diabetic animals. Additionally, they boost the activity of antioxidant enzymes like glutathione reductase, glutathione peroxidase, glutathione-S-transferase, and superoxide dismutase in diabetic animals. Compounds like phenolics and flavonoids found in mulberry leaves are excellent antioxidants, with chlorogenic acid being particularly effective against oxidative stress.

Mulberry leaves help reduce inflammation by targeting the NF-κB signaling pathway, which plays a role in inflammation caused by activated macrophages. They achieve this by decreasing the production of proinflammatory cytokines like iNOS, COX-2, TNF-α, IL-1β, and IL-6, which are regulated by NF-κB. Mulberry leaves also reduce the adhesion of monocytes to endothelial cells, a process induced by TNF-α. Overall, mulberry

leaves have a dose dependent anti-inflammatory effect.

Studies on humans have shown that mulberry leaves have both antioxidative and anti-inflammatory effects. In one clinical trial, patients with mild dyslipidemia who took mulberry leaf tablets containing DNJ for 12 weeks experienced a significant decrease in 8-isoprostane, a marker of oxidative damage. Their glutathione peroxidase activity also improved. Mulberry leaves also reduced peroxide levels in plasma, red blood cells, and urine after 4 weeks of treatment. Furthermore, mulberry leaves were effective in reducing small dense-LDL particles and lipids on red blood cell membranes, which are linked to oxidative damage, stiffening of blood vessel walls, and the formation of atherosclerotic plaques.

Anti-atherosclerosis

Mulberry leaves help prevent the development of atherosclerosis through various pathways. In lab tests, mulberry leaf extract reduces the oxidative modification of LDL particles and prevents their transfer through arterial walls, which is crucial in forming foam cells. It also inhibits the proliferation and movement of vascular smooth muscle cells, important in artery narrowing. Mulberry leaves restore normal levels of markers for endothelial dysfunction, such as sVCAM-1, fibrinogen and nitric oxide. These benefits are not only seen in the early stages of atherosclerosis but also effective even when plaques have formed. Long-term treatment with mulberry leaves significantly reduces plaque volume in animal studies.

Cardioprotective effect

Mulberry leaf administration in animal studies helped preserve cardiac structure and function. It reduced myocardial damage induced by isoproterenol (ISO), resulting in lower levels of cardiac markers and less myocarditis and myonecrosis compared to untreated animals. Mulberry leaves also maintained normal myocardial tissue structure, with fewer inflammatory cytokines and fibrous tissues in models of induced myocarditis. Additionally, the treatment improved cardiac hemodynamic function by reversing systolic and diastolic impairment, indicating protection against left ventricular remodeling development.

Impact of mulberry consumption

[15]Assessing the impact of mulberry consumption on cardiometabolic risk variables was the goal of this systematic review and meta-analysis. Several electronic databases were thoroughly searched for randomised controlled studies examining the impact of mulberry consumption. A higher amount of HDL cholesterol was also linked to mulberry eating. These results point to mulberry supplementation as a viable dietary intervention for those with metabolic problems and as a benefit for cardiometabolic health.

CONCLUSION

[1]According to the available evidence, mulberry consumption can provide favourable effects on HbA1C, some lipid profile parameters, and certain inflammatory markers compared to the control group. It seems that mulberry consumption is an appropriate strategy to reduce the risk of cardiometabolic diseases. However, further research is recommended to shed light on these findings.

[11]Mulberry is a key medicinal plant known for its bioactive compounds and strong antioxidant properties, making it valuable in treating diseases like cardiovascular conditions and cancer. It also helps prevent hyperlipidemia-related diseases and fatty liver disease by stimulating lipolysis and reducing lipid synthesis.

Mulberry also plays an important role in environmental safety and global food security. Sustainable agriculture practices like indoor hydroponics, aquaponics and aeroponics allow mulberry to be grown year-round, even in regions with unsuitable climates, poor soil, or limited land. These alternative farming methods can produce high yields without pesticides and with minimal water, making mulberry a versatile and valuable crop for various industries, including medicine, pharmacy and food production.

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CONFLICT OF INTEREST

I declare that I have no conflict of interest.

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