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ROLE OF MULBERRY LEAVES IN OXIDATIVE STRESS MANAGEMENT AND DIABETIC COMPLICATIONS

Rajeshwari Ullagaddi *

Department of Life Sciences, School of Science, Sri Sathya Sai University for Human Excellence, Navanihal, Kalaburagi, Karnataka – 585 313, India.
* Corresponding Author

ORCID Details: Dr Rajeshwari Ullagaddi: https://orcid.org/0009-0004-3533-3910

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, impaired insulin function, and altered carbohydrate, protein, and lipid metabolism. Oxidative stress plays a central role in the onset and progression of diabetic complications through excessive generation of reactive oxygen species (ROS) and reduced antioxidant defense systems. Natural plant-derived therapeutics have gained increasing attention due to their multi-targeted actions and minimal side effects. Among these, mulberry (Morus spp.) leaves have emerged as promising antidiabetic and antioxidant agents owing to their rich phytochemical composition, including flavonoids, alkaloids, polyphenols, vitamins, and minerals. Mulberry leaves exhibit significant free radical scavenging activity, inhibit lipid peroxidation, regulate glucose metabolism, and protect tissues against oxidative damage. Studies in experimental diabetic models have demonstrated their beneficial effects in preventing nephropathy, neuropathy, retinopathy, and cardiovascular complications. This review summarizes the biochemical mechanisms underlying oxidative stress in diabetes and critically discusses the role of mulberry leaves in mitigating diabetic complications through antioxidant and antihyperglycemic pathways.

Keywords: Mulberry Leaves, Oxidative Stress, Diabetes Mellitus, Antioxidants, Phytochemicals, Diabetic Complications, *Morus indica*, Reactive Oxygen Species.

1 INTRODUCTION

Diabetes mellitus is a global metabolic disorder with increasing prevalence that affects over 500 million people worldwide, and cases may surpass 780 million by 2045 (IDF, 2024) due to reduced pancreatic insulin secretion or ineffective action of insulin. Chronic hyperglycemia induces ROS due to various mechanisms, such as mitochondrial dysfunction, glucose autoxidation, the polyol pathway (both via aldose reductase and sorbitol), protein kinase C-mediated activation of several pathways, and AGE formation, which is in turn followed by irreversible damage to kidneys, retina, nerves, and blood vessels as well as the heart (Baynes, 1991; Brownlee et al., 2005). Antidiabetic drugs normalize blood sugar but have adverse effects and no protection against oxidative stress (Tiwari & Rao, 2002). Morus spp., as a medicinal plant, is considered favourable for safer and multifunctional benefits owing to bioactive compounds

like flavonoids, alkaloids, phenolic acids, polysaccharides, vitamins and minerals. Research suggests mulberry leaves increase insulin sensitivity, inhibit carbohydrate-hydrolysing enzymes, reduce oxidative damage, and protect against diabetic complications (Andallu & Varadacharyulu, 2002; Kimura et al., 2007). Molecular studies indicate that their effects include AMPK activation, modulation of the gut microbiota, inhibition of inflammatory pathways, attenuation of AGE-RAGE, and enhanced antioxidant defense.

Diabetes and its complications are characterized by increased oxidative stress. High blood sugar levels produce high levels of reactive oxygen species (ROS), which can overwhelm antioxidant defences and lead to cellular and tissue damage (Halliwell & Gutteridge, 2015). Chronic oxidative stress leads to endothelial dysfunction, inflammation, mitochondrial damage and cell death that drives the progression of nephropathy, neuropathy, retinopathy cardiovascular diseases and cataracts in diabetes (Forbes & Cooper 2013). Hyperglycemia also stimulates the production of inflammatory mediators such as NF-κB, TNF-α, and AGEs, leading to both aggravated tissue injury and metabolic imbalance (Brownlee, 2005). Although conventional antibiotics have been researched for microalgal toxicant, natural antioxidants which simultaneously act on diverse pathways have become a hot topic in recent years; mulberry (Morus spp.) The leaves are expected to have beneficial properties due to their antioxidant and antidiabetic activity. These are high in flavonoids (quercetin, rutin, kaempferol) and alkaloids (1-deoxynojirimycin, DNJ), which have the free radical scavenging; α–glucosidase inhibiting; anti-inflammatory; lipid-lowering effects (Asano et al., 2001; Kimura et al., 2007). Research in diabetic animal models indicate that supplementation with mulberry leaf has been shown to lower levels of lipid peroxidation, restore oxidative stress by antioxidant enzymes (SOD, CAT, GPx) activity and improve glycemic control (Andallu & Varadacharyulu, 2002). Introduction: With novel findings published till 2023, mulberry compounds have been revealed to modulate both AMPK and Nrf2 pathways, improve mitochondrial activities, regulate gut microbiota and inhibit oxidative-inflammatory cascades associated with insulin resistance along with complications generating clinically the much-desired ameliorating effects on T2DM (Zhang et al., 2025; Cheng et al., 2024). These results emphasize mulberry leaves as potential natural treatment for oxidative stress-related disease and diabetes control. This review aims to provide a comprehensive overview of oxidative stress in diabetes and critically evaluate the role of mulberry leaves in oxidative stress management and prevention of diabetic complications.

2 METHODOLOGY

This review collects the scientific literature on mulberry (Morus spp.) that helps mitigate oxidative stress and diabetic complications. Keywords such as “mulberry leaves,” “Morus indica,” “oxidative stress,” “diabetes mellitus,” “antioxidant activity,” “various phytochemicals,” diabetic complications, 1-deoxynojirimycin, and mulberry therapeutics were used for the selection of articles from PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and SpringerLink. This paper reviewed research from 1990 to 2026 that reported experimental, clinical, biochemical, and molecular findings. This research focuses on the phytochemical profile, oxidative stress pathways, and molecular mechanisms underlying the potential properties and therapeutic effects of mulberry leaf supplementation. The literature was grouped into sections on oxidative stress in diabetes, phytochemicals with antioxidant properties, associated mechanisms of action, and antidiabetic effects observed in complications, including animal studies and human data.

3 DIABETES MELLITUS AND OXIDATIVE STRESS

3.1 Pathophysiology of Diabetes Mellitus

Diabetes mellitus is a long-term metabolic condition which can be categorised as Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), gestational diabetes, and secondary diabetes. T1DM is due to autoimmune destruction which leads to insulin deficiency whereas in T2DM, there is development of insulin resistance with progressive β-cell dysfunction (American Diabetes Association, 2024). Insulin controls glucose by enhancing uptake in muscle and fat while downregulating glucose synthesis in the liver. Lack of insulin results in hyperglycemia, increased lipolysis, protein breakdown and disturbed energy metabolism. Chronic supervised hyperglycaemia activates biochemical pathways via polyol, protein kinase-C pathway (PKC), hexosamine biosynthesis pathway, AGE formation and elevated ROS in mitochondria (Brownlee 2005). Elevated ROS impair lipids, proteins, and DNA, leading to endothelial dysfunction, inflammation, vascular injury, and apoptosis, and initiating diabetic complications in different organs (Ullagaddi, 2025).

3.2 Oxidative Stress in Diabetes

Reactive oxygen species (ROS) are created due to oxidative stress when a cellular imbalance occurs between ROS production and the capacity of antioxidant defense mechanisms in the body. The main ROS are superoxide anions, hydroxyl radicals, hydrogen peroxide, singlet oxygen and peroxynitrite that usually act as signalling molecules for immunity and metabolism. Excess reactive oxygen species (ROS) can lead to damage in lipids, proteins, carbohydrates and DNA and ultimately compromise the cellular function (Halliwell & Gutteridge, 2015). In diabetes, ROS production is enhanced by high glucose due to glucose autoxidation (Kawamori et al., 2003), protein glycation (Pezzolesi et al., 2007), mitochondrial dysfunction (Nishikawa et al., 2000) (Figure 1).

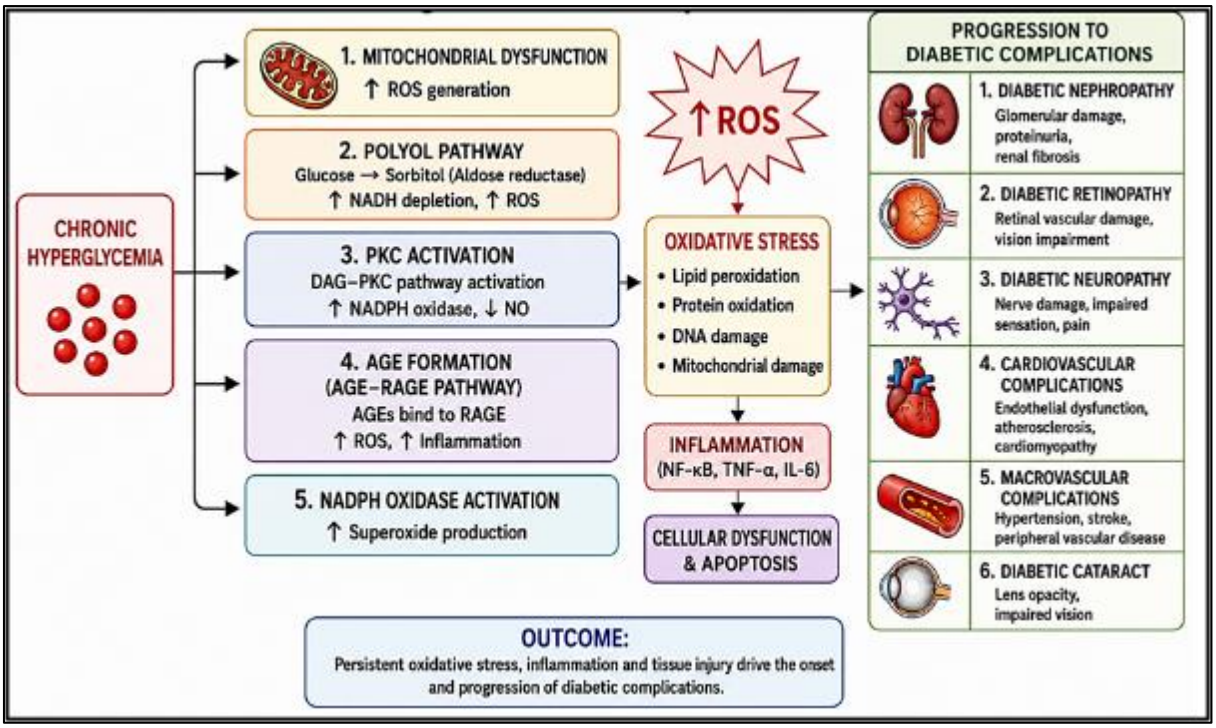

Figure 1: Oxidative stress pathways in diabetes and progression to diabetic complications.

NADPH oxidase activity and xanthine oxidases are major producers of the superoxide radical in various pathophysiological states close with electron leakage from mitochondria as one of the main sources of ROS generation (de Lema & Martín del Río, 2012). While high levels of ROS generate lipid peroxidation, protein oxidation, DNA damage, and mitochondrial failure, which leads to apoptosis and inflammation with elevated TNF-α and interleukins that aggravate the tissue injury and metabolic disorders (Baynes, 1991). These circumstances aggravate complications of diabetes such as nephropathy, retinopathy, neuropathy and cardiovascular diseases (Ullagaddi, 2025). As illustrated in Figure 1, chronic hyperglycaemia activates multiple biochemical pathways, including mitochondrial dysfunction, the polyol pathway, PKC activation, AGE–RAGE signalling and NADPH oxidase activity, collectively resulting in excessive ROS generation and subsequent oxidative and inflammatory tissue damage.

3.3 Lipid Peroxidation and Cellular Damage

Lipid peroxidation is one of the major deleterious effects of oxidative stress in diabetes mellitus and is thought to be a significant contributor to the development of diabetic complications (Baynes, 1991; Halliwell & Gutteridge, 2015). Reactive oxygen species (ROS) directly lesion polyunsaturated fatty acids within cellular and organelle membranes, resulting in lipid peroxides and reactive aldehydes, including malondialdehyde (MDA) and 4-hydroxynonenal (HNE) (Halliwell & Gutteridge, 2015). These deleterious nucleotide and protein metabolites disrupt membrane fluidity and integrity, decrease activity of membrane-bound enzymes, modify ion transport mechanisms, and alter intracellular signaling pathways (Bandyopadhyay et al., 1999). In hyperglycemic conditions, common findings in diabetic patients and experimental diabetic models include high concentrations of thiobarbituric acid reactive substances (TBARS) and MDA in clinical samples, suggesting increased lipid peroxidation (Andallu & Varadacharyulu, 2002; Kumari & Augusti, 2002). Increased lipid peroxidation is clearly related to vascular dysfunction, diabetic neuropathy, nephropathy, retinopathy, and cataract (Baynes 1991; Forbes & Cooper 2013).

Oxidative stress also leads to extensive protein oxidation and cross-linking with carbonyl derivatization and chopped peptide chains due to enzyme inactivation and changes the receptor function (Telci et al., 2000). Oxidative stress modifies structural and enzymatic proteins, contributing to impaired cellular metabolism and playing a central role in tissue dysfunction in diabetes. Beyond that, ROS-induced oxidative damage leads to nucleic acid DNA strand breaks and mitochondrial mutations, for example, also impaired DNA repair mechanisms, promoting mitochondrial dysfunction and apoptosis (Hunt et al., 1988; Brownlee, 2005). Oxidative stress further activates inflammatory signaling pathways involving transcription factors (such as nuclear factor-kappa B [NF-κB]), resulting in the production of inflammatory cytokines (e.g., tumour necrosis factor-alpha [TNF-α] and interleukins), causing persistent cellular injury and chronic inflammation in diabetic tissues (Manna et al., 1998; Forbes & Cooper, 2013). These synergistic oxidative and inflammatory processes are the common pathway in the course of long-term diabetic complications.

4 DIABETIC COMPLICATIONS ASSOCIATED WITH OXIDATIVE STRESS

Diabetic vascular and non-vascular complications are one of the major causes of morbidity/disability/mortality in patients with diabetes, and they are mostly due to oxidative stress, inflammation, endothelial dysfunction, and metabolic disturbances caused by chronic hyperglycaemia (Brownlee 2005; Forbes & Cooper 2013). Continued increases in blood sugar levels lead to unregulated production of reactive oxygen species (ROS), activation of inflammatory mediators, generation of advanced glycation end products (AGEs) and permanent damage to the antioxidant defence mechanism, finally causing progressive tissue and organ derangement (Brownlee, 2005). Diabetic complications can be classified into micro- and macrovascular conditions: nephropathy, neuropathy, retinopathy, and cardiovascular and cerebrovascular diseases. Oxidative stress is central to the pathophysiological mechanisms underlying the development and progression of these complications, through its ability to induce lipid peroxidation, mitochondrial dysfunction, vascular injury, and cellular apoptosis.

4.1 Diabetic Nephropathy

Diabetic nephropathy is the most serious microvascular complication of diabetes mellitus and a common cause of end-stage renal disease worldwide (Forbes & Cooper, 2013). It is characterized by the presence of persistent albuminuria, glomerular hypertrophy, thickening of the GBM, mesangial expansion, and a progressive decline in renal function. Studies have shown that hyperglycaemia-induced oxidative stress contributes to diabetic nephropathy pathogenesis through ROS production in renal tissue.

Elevated glucose promotes several biochemical pathways, including the polyol pathway, protein kinase-C activation, and AGE formation (Brownlee, 2005), which, in turn, increases oxidative stress levels and inflammation processes in renal cells. ROS injure glomerular endothelial cells, podocytes and tubular epithelial cells to cause abnormal filtration with proteinuria. According to Forbes et al. (2013), oxidative stress also stimulates secretion of transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and inflammatory cytokines that promote fibrosis and matrix deposition.

Diabetic nephropathy is associated with increased lipid peroxidation and decreased activity of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Baynes, 1991). Further oxidative damage aggravates renal inflammation, apoptosis, and sclerosis. Antioxidants and phytochemicals have been shown to reduce oxidative stress-mediated renal injury and improve kidney function in diabetic models (Andallu & Varadacharyulu 2002).

4.2 Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular retinal disease due to diabetes and one of the most common causes of blindness in diabetic patients worldwide (Cheung et al., 2010). Hyperglycaemia induces oxidative stress in retinal tissues, culminating in retinal endothelial dysfunction, pericyte loss, retinal ischemia, vascular leakage and neovascularization. Excessive ROS production causes lipid peroxidation, protein oxidation, mitochondrial dysfunction, and apoptosis in retinal cells (Kowluru & Chan, 2007). Oxidative stress activates inflammatory pathways and transcription factors, including NF-κB and vascular endothelial growth factor (VEGF), resulting in retinal inflammation, oedema, haemorrhage and abnormal blood vessel formation (Brownlee, 2005). Retinal tissues become saturated with advanced glycation end products, which perpetuate oxidative injury and inflammatory signaling. Reactive oxygen species (ROS) are generated from damaged mitochondrial DNA, inhibiting ATP synthesis and promoting retinal cell death (Kowluru & Mishra, 2015). Inadequate antioxidant defenses and impaired glutathione metabolism are additional factors increasing the susceptibility of retinal tissues to oxidative injury (Andallu & Varadacharyulu 2002).

4.3 Diabetic Neuropathy

Diabetic neuropathy is the most common complication of diabetes with pernicious autonomic & peripheral nervous system (PNS) involvement. It is a type of neuropathy, which involves degeneration of nerve fibers, resulting in slowed or lost nerve conduction velocity, numbness or tingling sensations and/or pain, and muscle weakness (Vinik et al., 2013). Increased oxidative stress is also thought to be a principal factor in neuronal damage in diabetic neuropathy. Hyperglycemic chronicity stimulates excessive production of ROS in neurons within the mitochondria, triggering oxidative damage, reduced ATP-producing activity, and axonal loss (Vincent et al., 2004). Formation of sorbitol as a result of the polyol pathway can lead to intracellular osmotic pressure and intracellular myoinositol depletion in nerve cells. Lipid peroxidation: Impairs neuronal membrane integrity and disrupts neurotransmission; oxidative modification of proteins: Impairs neuronal enzyme function and ion channel activity. Reactive oxygen species (ROS) also induce the expression of inflammatory cytokines and activate NF-κB signaling pathways, which leads to chronic neuroinflammation and neuronal apoptosis. This leads to a compensatory down-regulation of antioxidant defense mechanisms and renders neurons increasingly susceptible to oxidative stress-mediated injury. The combined impact of

these pathophysiological processes leads to sensory deficits, autonomic dysfunction, and progressive nerve degeneration evident in diabetic neuropathy.

4.4 Cardiovascular Complications

Cardiovascular events are the primary cause of deaths in diabetic patients and encompass coronary artery disease, hypertension, peripheral vascular disease, and stroke (Low Wang et al., 2016). Hyperglycemia-related oxidative stress plays a major role in endothelial dysfunction, followed by vascular inflammation and atherosclerotic plaque formation. Excess ROS diminishes nitric oxide bioavailability, induces endothelial dysfunction, and damages the endothelium. Oxidative modification of low-density lipoproteins (LDL) and foam cell formation contribute to atherosclerosis (Forbes & Cooper, 2013). Hyperglycaemia also triggers the activation of inflammatory cytokines, adhesion molecules, and prothrombotic factors implicated in vascular occlusion and thrombosis. Inhibition of these enzymes leads to mitochondrial and lipid peroxidation-mediated injury to cardiac tissue and blood vessels. Typical dyslipidemia of diabetes is characterized by hypertriglyceridemia, increased LDL cholesterol, and decreased HDL cholesterol, which increases cardiovascular risk. Chronic oxidative stress also plays a part in myocardial fibrosis, reduced cardiac contractility, and diabetic cardiomyopathy (Andallu & Varadacharyulu 2002).

4.5 Cataract Formation

Cataract formation is the most common ocular complication of diabetes, in which clouding and opacification of the lens module result in defective light vision and, ultimately, blindness. The two important causes for diabetic cataractogenesis include oxidative stress induced by hyperglycemia and activation of the polyol pathway (Obrosova et al., 2010). In lens cells, aldose reductase converts increased intracellular glucose into sorbitol, leading to osmotic stress, cellular swelling, and membrane damage. In contrast, ROS-mediated oxidation of lens proteins leads to crystallin aggregation and loss of lens transparency (Spector et al., 1995). Depletion of glutathione and lipid peroxidation causes additional oxidative damage to the antioxidant defense systems in the lens. Oxidative stress can also induce apoptosis and structural damage of lens epithelial cells, which could lead to mitochondrial damage. Continuous oxidative damage leads to cataract development and compromised vision in individuals with diabetes.

5 MULBERRY (MORUS SPP.): BOTANICAL AND NUTRITIONAL OVERVIEW

Mulberry (Morus spp.) is a perennial evergreen in the family *Moraceae* and is widely cultivated in Asian countries such as India, China, Japan, and Korea. The most widely cultivated mulberry species are Morus indica, Morus alba, Morus nigra, and Morus laevigata (Andallu & Varadacharyulu, 2002). Mulberry plants are widely used in sericulture and serve as a primary food source for silkworms (Bombyx mori). Regardless of their importance as an agricultural crop, mulberry leaves, fruits, roots, and bark are a source of an extensive range of biological activities and represent highly medicinal and nutritional values that have been used in traditional systems of medicine to treat diabetes mellitus, hyperlipidemia, hypertension, inflammation, liver disorder, and cardiovascular disease.

Mulberry leaves are nutritionally significant, including proteins, dietary fibre, carbohydrates, and essential amino acids, as well as vitamins and minerals, including bioactive phytochemicals. The leaves contain calcium, potassium, magnesium, phosphorus, zinc, iron, selenium (a trace element), and chromium, which support the physiological & metabolic functions of these minerals (Andallu and Varadacharyulu, 2002). Furthermore, vitamins, including β-carotene, vitamin C, riboflavin, niacin, biotin, and folic acid or B-complex vitamins with antioxidant action, are also found in mulberry leaves. Because of the nutritional richness and pharmacological importance of mulberry leaves, their use as functional foods and nutraceuticals is widely accepted. Bioactive compounds from mulberry leaves have shown various pharmacological effects, including antihyperglycemic, antihyperlipidemic, antioxidant, anti-inflammatory, and hepatoprotective/nephroprotective/neuroprotective/cardioprotective activities, in many studies. These health-promoting attributes mainly stem from the distribution of diverse bioactive compounds across phytochemical groups such as phenolic acids, flavonoids, alkaloids, polyphenols, polysaccharides, and sterols. Owing to their safety, high nutritional value, and therapeutic potential, mulberry leaves are being more frequently utilized in herbal tea, dietary supplements, powder products, biscuits/capsules, and functional beverages.

6 PHYTOCHEMICAL CONSTITUENTS OF MULBERRY LEAVES

Mulberry (Morus spp.) leaves are significant reservoirs of biologically active phytochemicals that contribute to their antioxidant, antihyperglycemic, anti-inflammatory, and therapeutic potential worldwide. They contain flavonoids, alkaloids, polyphenols, polysaccharides, phenolic acids, and phytosterols, along with vitamins and minerals, as well as amino acids and volatile compounds (Andallu & Varadacharyulu, 2002; Asano et al., 2001). Flavonoids such as quercetin, rutin, kaempferol, isoquercetin, astragalin, and quercetin glycosides are among the most important antioxidants because of their free-radical scavenging and metal-chelating effects (Sharma et al., 2000). These flavonoids have been shown to prevent lipid peroxidation, reduce oxidative stress, enhance endothelial function, and down-regulate pro-

inflammatory signaling pathways associated with diabetic complications. Polyphenolic compounds such as chlorogenic acid, caffeic acid, gallic acid, catechins, and anthocyanins, which exhibit potent antioxidant and anti-inflammatory activities by scavenging ROS and inhibiting the formation of advanced glycation end products (AGEs), are also present abundantly in mulberry arborescent leaves (Halliwell & Gutteridge, 2015). The recent research also showed that mulberry polyphenols modulated AMP-activated protein kinase (AMPK) and nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathways, suggesting up-regulating endogenous antioxidant defense and glucose metabolism (Zhang et al., 2025). Another group of phytochemicals abundant in mulberry leaves is alkaloids, and one of them, 1-deoxynojirimycin (DNJ), is a powerful natural α-glucosidase inhibitor (Kimura et al., 2007). DNJ delays carbohydrate digestion in the intestine and glucose absorption, lowering postprandial hyperglycemia. These effects are linked to glycosidase inhibition and glucose regulation by other alkaloids such as fagomine, N-methyl-DNJ, and calystegines. Besides the alkaloids and flavonoids, mulberry leaves also have bioactive polysaccharides that show antioxidant, immunomodulatory, and antidiabetic effects by improving insulin sensitivity, decreasing inflammation cytokines, and increasing non-enzymatic antioxidant SOD, CAT GPx activities (Asano et al., 2001). The major bioactive constituents of mulberry leaves, their representative compounds, biological actions, molecular targets, and potential benefits in diabetes and oxidative stress management are summarized in Table 1.

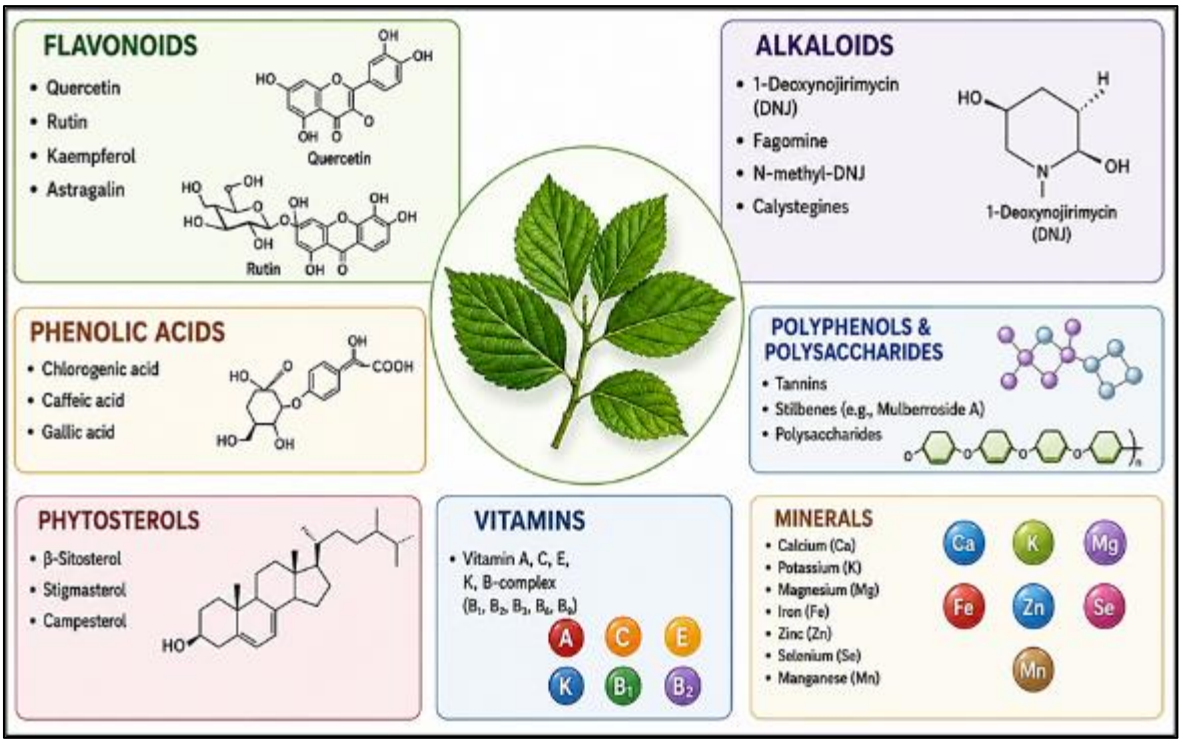

Figure 2: Major phytochemical constituents of mulberry leaves (Morus spp.).

Table 1: Major bioactive constituents of mulberry leaves and their proposed roles in diabetes and oxidative-stress management

Bioactive constituent/group	Representative compounds	Major biological actions	Relevant molecular/pathophysiological targets	Potential benefits in diabetes
Flavonoids	Quercetin, rutin, kaempferol, astragalin	Free-radical scavenging; inhibition of lipid peroxidation; anti-inflammatory activity	Nrf2, AMPK, NF-κB; oxidative-stress pathways	Reduced oxidative damage, improved glucose metabolism, protection of vascular and pancreatic tissues
Alkaloids	1-Deoxynojirimycin (DNJ), fagomine, N-methyl-DNJ, calystegines	Inhibition of carbohydrate digestion and glucose absorption	α-Glucosidase and other glycosidases	Reduced postprandial hyperglycaemia and improved glycaemic control
Phenolic acids	Chlorogenic acid, caffeic acid, gallic acid	Antioxidant and anti-inflammatory effects; free-radical scavenging	ROS-related pathways; inflammatory signalling; AGE formation	Reduction of oxidative damage and inflammation associated with chronic hyperglycaemia
Polyphenols	Catechins, anthocyanins and other polyphenolic compounds	Antioxidant, anti-inflammatory and antiglycation activities	Nrf2, NF-κB and AGE-RAGE pathways	Reduced oxidative stress, inflammation and cellular injury
Polysaccharides	Mulberry leaf polysaccharide fractions	Antioxidant, immunomodulatory and metabolic effects	Antioxidant defence and glucose-regulatory pathways	Improved antioxidant enzyme activity and metabolic regulation
Phytosterols	β-Sitosterol, stigmasterol, campesterol	Lipid-modulating and potentially antioxidant effects	Hepatic lipid metabolism and cholesterol homeostasis	Reduction of dyslipidaemia and cardiovascular risk
Vitamins	Vitamins A, C, E and B-complex vitamins	Antioxidant activity and metabolic support	Endogenous antioxidant defence and cellular metabolism	Protection against oxidative damage and support of metabolic homeostasis
Minerals	Calcium, potassium, magnesium, iron, zinc, selenium, chromium	Cofactors in antioxidant defence and metabolic processes	Antioxidant enzymes, insulin signalling and cellular metabolism	Support of antioxidant capacity, insulin function and metabolic regulation
Combined phytochemical matrix	Flavonoids + alkaloids + phenolics + polysaccharides + micronutrients	Multi-target antioxidant, antihyperglycaemic, antihyperlipidaemic and anti-inflammatory effects	AMPK, Nrf2, NF-κB, AGE-RAGE, mitochondrial function and gut microbiota	Integrated improvement of glycaemic control, oxidative balance, inflammation and protection against diabetic complications

Additionally, mulberry leaves are rich in vitamins: β-carotene, vitamin C, riboflavin, niacin and folate, as well as a plethora of trace metals such as calcium, magnesium, potassium, zinc, selenium, chromium, and iron that help in antioxidant defense, insulin signalling, and metabolic regulation (Andallu & Varadacharyulu 2002). The synergistic interaction between these phytochemicals and micronutrients could support antioxidant therapy or prevent diabetic complications by modulating oxidative stress. The diverse phytochemical composition of mulberry leaves is summarized in Figure 2, highlighting the major classes of bioactive compounds associated with their antioxidant, antihyperglycemic, anti-inflammatory, and metabolic effects.

7 ANTIDIABETIC PROPERTIES OF MULBERRY LEAVES

Mulberry (Morus spp.) leaves have significant antidiabetic activity and involve multiple metabolic pathways that regulate glucose homeostasis and diabetic complications, leading scientists to focus research on this aspect. Unlike many synthetic antidiabetic agents that target single biochemical pathways, mulberry leaves offer a broader therapeutic profile by inhibiting carbohydrate digestion and glucose absorption, improving insulin sensitivity, modulating enzymes involved in glucose metabolism, and suppressing oxidative stress and chronic inflammation. The health-promoting effects of plant foods can primarily be attributed to functional compounds, including flavonoids, alkaloids, polyphenols, polysaccharides, phytosterols, vitamins, and minerals. Several experimental and clinical trials showed that supplementation of mulberry leaf is an effective agent for lowering fasting and postprandial blood glucose and glycosylated haemoglobin (HbA1c) improving antioxidant capacity along with delaying progression of diabetic complications such as nephropathy and neuropathy, as well as cardiovascular disorders (Tiwari & Rao 2002). However, recent molecular investigations show that mulberry phytochemicals regulate signalling pathways related to insulin action, mitochondrial function, oxidative stress, and inflammatory responses. The multifaceted antidiabetic mechanisms of mulberry leaves, including inhibition of carbohydrate-digesting enzymes, improvement of insulin sensitivity, activation of AMPK signalling, regulation of glucose metabolism, antihyperlipidemic effects, anti-inflammatory activity, and protection of pancreatic β-cells, are summarized in Figure 3.

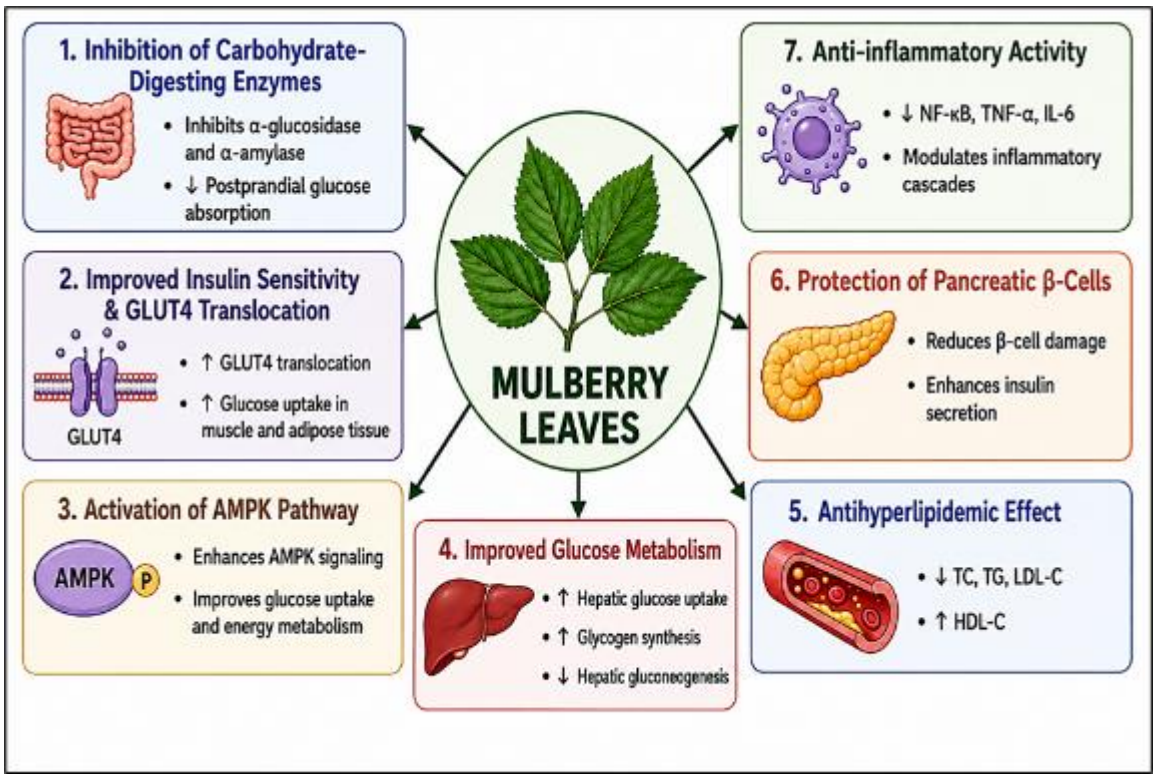

Figure 3: Multifaceted antidiabetic mechanisms of mulberry leaves.

7.1 Inhibition of α-Glucosidase Activity

The inhibition of intestinal α-glucosidase enzymes, which regulate the digestion of complex carbohydrates into absorbable glucose, is one of the main antidiabetic mechanisms of mulberry leaves. Bioactive alkaloids in mulberry leaves, including potent α-glucosidase inhibitors such as 1-deoxynojirimycin (DNJ), fagomine, and calystegines, strongly suppress α-glucosidase activity and delay glucose absorption into the intestine (Asano et al., 2001; Kimura et al., 2007). This delayed absorption significantly reduces postprandial hyperglycemia and results in minimal sudden changes in blood glucose levels. In contrast to some synthetic α-glucosidase inhibitors such as acarbose, mulberry-derived

compounds are considered safer and commonly associated with a lower incidence of gastrointestinal adverse reactions. Moreover, sustained maintenance of postprandial glucose levels mitigates pancreatic strain, increases insulin sensitivity, and lowers the risk of chronic hyperglycemia and the subsequent vascular damage mediated by oxidative stress.

7.2 Regulation of Glucose Metabolism

Phytochemicals from mulberry leaves can increase the capacity of glucose utilisation and decrease blood glucose level through the regulation of key enzymes in glucose metabolism. Experimental studies have shown that mulberry supplementation increased the activity of glycolytic enzymes such as hexokinase, phosphofructokinase, and pyruvate kinase but inhibited gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase in diabetic models (Andallu & Varadacharyulu, 2002). And it stimulates glucose oxidation and glycogen synthesis, while inhibiting excessive hepatic glucose production. In addition, the flavonoids and polyphenols in mulberry leaves activate the AMP-activated protein kinase (AMPK) signalling pathway, promote GLUT4 translocation, and increase insulin-mediated glucose uptake by skeletal muscle and adipose tissues (Zhang et al. 2025). This is complimented by enhanced mitochondrial bioenergetics along with reduced oxidative stress to improve glucose homeostasis and metabolic integration in diabetic states (Ullagaddi, 2025).

7.3 Protection of Pancreatic β-Cells

The various antioxidant, anti-inflammatory and cytoprotective properties of mulberry leaves play a strong role in protecting β-cells. Bioactive flavonoids and polyphenols in mulberry leaves decreased the generation of reactive oxygen species (ROS), inhibited lipid peroxidation, and improved antioxidant enzyme activities such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), thus protecting β-cells from oxidative injury (Baynes, 1991; Andallu & Varadacharyulu, 2002). Studies on the histopathology of streptozotocin (STZ)-induced diabetic rats showed that mulberry leaf maintains pancreatic islet architecture and prevents β-cell degeneration. Recent molecular studies have also indicated that the phytochemicals in mulberry activate Nrf2-mediated antioxidant pathways, inhibit mitochondrial apoptosis signaling, and suppress pro-inflammatory cytokines such as TNF-α and interleukins, which contribute to improving insulin secretion and protecting β-cell survival (Andallu & Varadacharyulu, 2002).

7.4 Improvement of Insulin Sensitivity

Type 2 diabetes mellitus is associated with insulin resistance, which plays a major role in its pathogenesis and causes prolonged hyperglycemia and metabolic dysfunction. The multiple systems-wide mechanisms underlying the multiple effects of mulberry leaves on the improvement of insulin sensitivity include attenuation of oxidative stress, downregulation of inflammatory mediators, enhancement of signaling via the insulin receptor, and regulation of glucose transporter activity. Mulberry leaves also increase insulin receptor phosphorylation (as well as glucose uptake via GLUT4-mediated transport) in peripheral tissues, including adipose tissue and skeletal muscle, through the combined effects of flavonoids and polyphenols that are present in mulberry leaves. Moreover, mulberry phytochemicals suppress circulating levels of inflammatory cytokines, such as TNF-α and IL-6, which interfere with the insulin signalling cascade. Recent studies have also indicated that the protective effect of mulberry leaf extracts is associated with improved gut microbiota composition and increased short-chain fatty acid (SCFA) production, which improve metabolic homeostasis, insulin sensitivity, and systemic anti-inflammatory responses (Cheng et al., 2024). These synergistic effects improve glucose tolerance and reduce insulin resistance in diabetes.

7.5 Antihyperlipidemic Effects

Diabetes mellitus can be often associated with dyslipidemia, which is characterized by hypertriglyceridemia, increased low-density lipoprotein (LDL) cholesterol, and reduced high-density lipoprotein (HDL) cholesterol levels along with more lipid peroxidation thereby increasing the cardiovascular risk significantly. Mulberry leaves are also known to have powerful antihyperlipidemic properties exerting beneficial effects on the lipid profile of experimental diabetic models (Andallu & Varadacharyulu, 2002). Supplementation with mulberry results in a remarkable molal decrease in serum triglycerides, total cholesterol, LDL cholesterol and very low-density lipoproteins (VLDL) and increase protective HDL cholesterol. The lipid-lowering effects of these components are largely due to flavonoids, phytosterols, dietary fiber, and polyphenolic compounds that inhibit lipid synthesis, suppress LDL oxidation, and improve hepatic lipid metabolism. Moreover, antioxidant activity of mulberry leaves alleviates lipid peroxidation and protects vascular tissues against oxidative damage; as a result, promoting the risk of development of atherosclerosis, endothelial dysfunction, and cardiovascular complications in diabetic patients.

7.6 Anti-inflammatory and Cytoprotective Effects

Insulin resistance, β-cell dysfunction and the progressive worsening of diabetic complications have strong ties to persistent low-intensity inflammation and oxidative stress. Flavonoid, polyphenols, alkaloids and antioxidant vitamins contained in Mulberry leaves exhibited potent anti-inflammatory and cytoprotective activities [15]. Evidence showed that the phytochemicals suppress activation of the nuclear factor-kappa B (NF-κB) inflammatory transcription factors, and reduce pro-inflammatory cytokines production such as tumor necrosis factor-alpha (TNF-α) and interleukins, as well as cyclooxygenase enzymes (Brownlee, 2005). This helps in the progression of diabetes because many cytokines downregulate endothelial function, apoptosis and the processes of tissue injury and fibrosis. The major molecular mechanisms underlying the antidiabetic and antioxidant activities of mulberry leaves, including α-glucosidase inhibition, enhanced GLUT4-mediated glucose uptake, AMPK activation, modulation of hepatic glucose metabolism, antihyperlipidemic activity, antioxidant defence, anti-inflammatory effects, and pancreatic β-cell protection, are collectively illustrated in Figure 5.

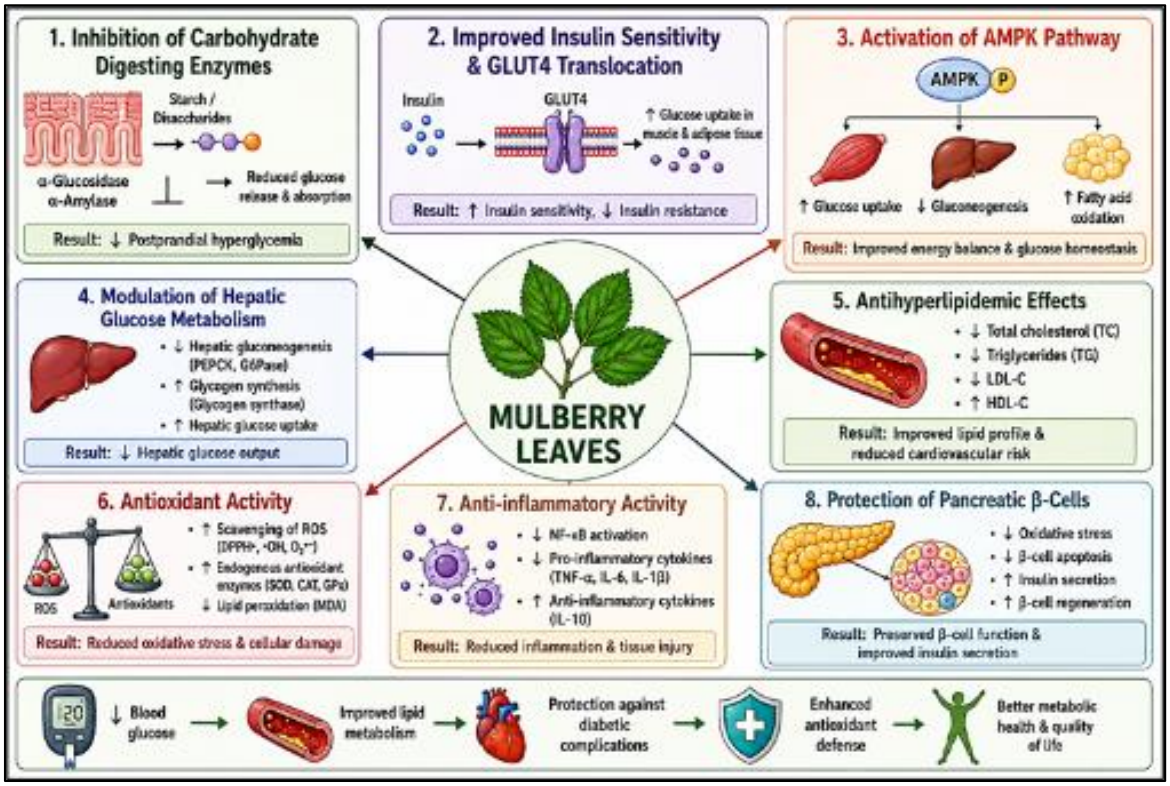

Figure 5: Molecular mechanisms underlying the antidiabetic and antioxidant activities of mulberry leaves.

Moreover, mulberry phytochemicals hold up the integrity of the mitochondria, optimize endogenous antioxidant defense systems, minimize oxidative damage to cellular membranes and proteins, and protect renal, neural, retinal, hepatic and cardiovascular tissues against chronic hyperglycemia-induced injury. Together, these dual antioxidant and anti-inflammatory properties play an important role in preventing and treating diabetic complications.

8 ROLE OF MULBERRY LEAVES IN DIABETIC COMPLICATIONS

Cerebrovascular and cardiovascular disorders, renal disease, retinopathy, neuropathies are the complications arising mainly from hyperglycemia induced vascular inflammation as well as progression of metabolic derangements which damage multiple organs. Continuous excessive generation of reactive oxygen species (ROS) leads to the activation of multiple pathological pathways including lipid peroxidation, formation of advanced glycation end products (AGE), mitochondrial dysfunction, production of inflammatory cytokines and apoptosis contributing to development of nephropathy, neuropathy, retinopathy cardiovascular diseases and cataracts; The continual excessive generation of ROS activates multiple pathological pathways that contribute to the development kidney injury. Mulberry (Morus spp.) has been shown to be very effective in protecting against diabetic complications through their antioxidant, anti-inflammatory, antihyperglycemic, and antihyperlipidemic effects. The broad range of phytochemicals in mulberry leaves, such as flavonoids, alkaloids, polyphenols, polysaccharides, vitamins, and minerals, work together as antioxidants that improve glucose metabolism, reduce oxidative stress, decrease haemoglobin glycation, and protect cell integrity from diabetes mellitus-related injuries. As illustrated in Figure 4, the bioactive compounds of mulberry leaves are absorbed and distributed systemically, where they exert protective effects on multiple organs, including the

kidneys, eyes, nervous system, heart, and pancreas, through antioxidant, anti-inflammatory, antihyperglycemic, and cytoprotective mechanisms.

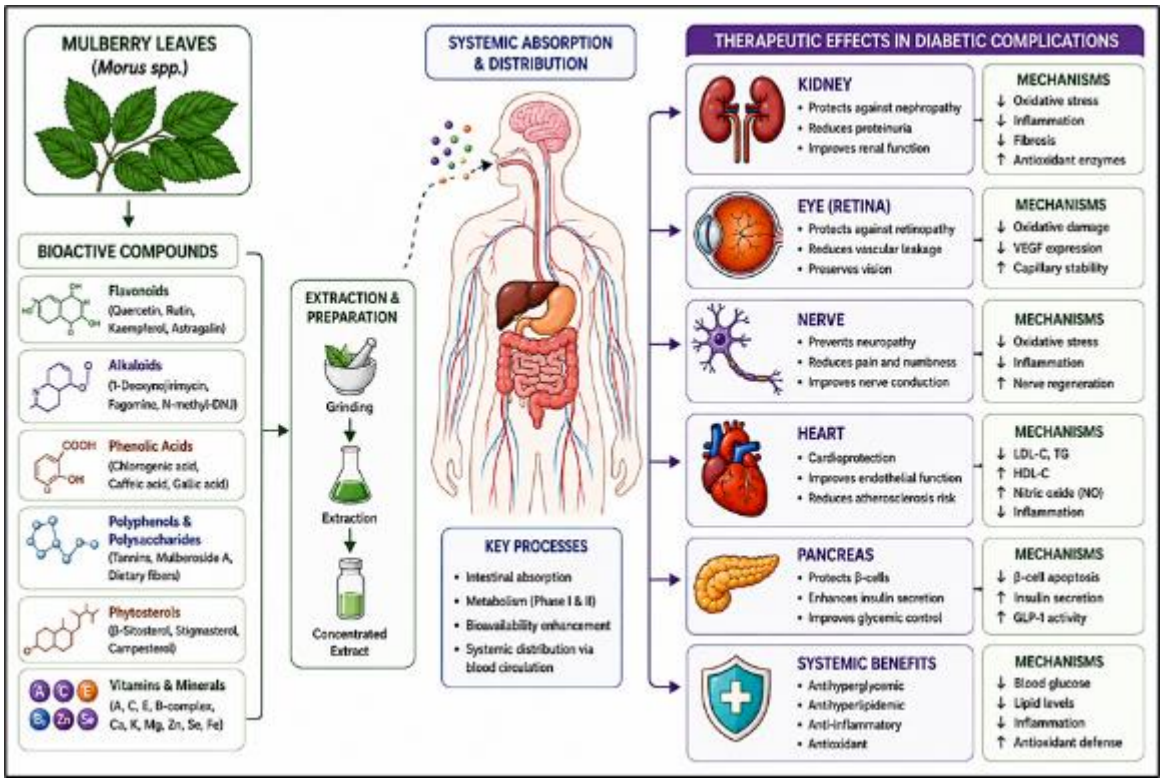

Figure 4: Systemic distribution and protective effects of mulberry leaf bioactives against diabetic complications.

8.1 Nephroprotective Effects

Diabetic nephropathy is among the most devastating microvascular complications of diabetes, which is characterised by albuminuria, glomerular hypertrophy, renal fibrosis, and progressive loss of kidney function. High levels of glucose lead to oxidative stress and thus damage glomerular endothelial cells, podocytes and renal tubules by the generation of reactive oxygen species (ROS), lipid peroxidation, inflammatory cytokines production, and extra-cellular matrix accumulation (Forbes & Cooper 2013). Furthermore, mulberry leaves exhibited marked nephroprotective benefits by strengthening the antioxidant defense systems in the kidneys and reducing oxidative stress. Evidence from experimental studies also showed that mulberry leaf supplementation lowers tissue and serum markers of lipid peroxidation, increases antioxidant enzyme activities (the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), and decreases levels of serum creatinine, urea and renal oxidative damage in diabetic rats. Moreover, mulberry phytochemicals inhibit pro-inflammatory mediators and the TGF-β signalling pathway implicated in fibrosis, thereby attenuating renal inflammation and structural damage. The combined antioxidant and antihyperglycemic actions of mulberry leaves on these processes help maintain kidney function and slow the progression of diabetic nephropathy.

8.2 Retinoprotective Effects

Abstract: Diabetic retinopathy is a progressive retinal microvascular complication of diabetes and the leading cause of blindness globally in working-age members of the population. Chronic hyperglycemia increases oxidative stress in retinal tissues, leading to endothelial dysfunction, thickening of the capillary basement membrane, retinal ischemia, plasma leakage, and abnormal angiogenesis (Kowluru & Chan 2007). A lot of ROS generation cause retinal nerve and vascular cell death by lipid peroxidation & mitochondrial dysfunction, protein oxidation and inflammatory signalling. Mulberry leaves exhibit potent retinoprotective activity against oxidative and inflammatory damage induced by the same stressors in retinal photoreceptors, achieved through their phytochemical composition (e.g., quercetin, rutin, chlorogenic acid, anthocyanins with demonstrated antioxidant and anti-inflammatory activities). The antioxidant and anti-inflammatory properties of these compounds enable them to scavenge ROS, inhibit lipid peroxidation, suppress NF-κB and VEGF-mediated inflammatory pathways, and protect retinal cells against oxidative injury. Moreover, mulberry phytochemicals augment endogenous antioxidant defences and ameliorate mitochondrial homeostasis in retinal tissues, thereby mitigating retinal dysregulation and vascular deficits that complicate diabetic retinopathy. This may also contribute to the neuroprotective effects of mulberry polyphenols in preserving retinal structure and visual

function under diabetic conditions, recent studies suggesting that they exhibit anti-inflammatory and anti-apoptotic actions.

8.3 Neuroprotective Effects

Diabetic neuropathy (DN) is one of the most common chronic complications in diabetes, which is characterized as degeneration of nerve fibers, conduction impairment, sensory deficit (e.g., numbness and pain), and autonomic dysfunction. Oxidative stress plays a major role in the pathophysiology of diabetic neuropathy through mitochondrial dysfunction, lipid peroxidation, production of inflammatory cytokines, and neuronal apoptosis (Vincent et al., 2004). Hyperglycemia further exacerbates neuronal damage and vascular dysfunction through the activation of the polyol pathway and AGEs production. Mulberry leaves show a substantial neuroprotective role in oxidative stress, stopping neuronal cell membrane disintegration and recovering antioxidant defense systems. Abstract: This study examined the hypoglycemic and antioxidant activity of mulberry leaves (Morus alba L.) in normal male rats to explain phenotypic variations through vegetation composition among different populations. Flavonoids and polyphenols are important bioactive compounds that suppress ROS generation, inhibit lipid peroxidation, and enhance activities of antioxidative enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in neural tissues. Moreover, mulberry phytochemicals decrease pro-inflammatory cytokines that contribute to neuroinflammation and neuronal degeneration, including TNF-α and IL-6. More importantly, glucose regulation and mitochondrial function has also improved, thus supporting neuronal survival and nerve conduction. These synergistic antioxidant, anti-inflammatory, and cytoprotective actions serve to reduce neuropathic symptoms and slow the progression of diabetic neuropathy.

8.4 Cardioprotective Effects

Cardiovascular complications are the primary cause of death in diabetic patients and include atherosclerosis, coronary artery disease, hypertension, myocardial infarction and stroke. Endothelial dysfunction, vascular inflammation, lipid abnormalities and atherosclerotic plaque formation are mediated largely by the oxidative stress prolonged due to hyperglycaemia (Low Wang et al., 2016). ROS reduces nitric oxide availability and vascular relaxation, facilitates LDL oxidation, and contributes to atherosclerotic vascular damage and thrombosis. Mulberry leaves show strong cardioprotective activity, mainly due to antioxidative and down-regulatory effects on hyperlipidaemia and inflammation, respectively. Mulberry supplementation was also shown to significantly decrease serum triglycerides, total cholesterol, LDL cholesterol, and lipid peroxidation and to increase HDL cholesterol in animal models of diabetes (Andallu & Varadacharyulu, 2002). Flavonoid compounds (e.g., quercetin and rutin) block LDL oxidation, inhibit inflammatory signalling pathways, enhance endothelial dysfunction, and decrease vascular injury induced by oxidative stress. Moreover, mulberries' phytochemicals enhance mitochondrial energy metabolism and mitigate cardiac inflammation and fibrosis, both of which protect against diabetic cardiomyopathy and cardiovascular dysfunction.

8.5 Protects against cataract formation

Cataract formation is one of the most frequent ocular complications of diabetes, with lens opacification leading to a progressive visual impairment over time. Sorbitol accumulation, an osmotic stress that produces oxidative damage and promotes protein aggregation in the lens as a result of excessive stimulation of the polyol pathway by chronic hyperglycaemia, happens in lens cells (Obrosova et al., 2010). Lens opacity and cataract progression are also exacerbated by ROS-mediated oxidation of crystallin proteins and by depletion of the antioxidant glutathione. The antioxidant activity of mulberry leaves and their reduction of oxidative stress in lens tissues result in protective effects against diabetic cataract formation. In diabetic rats, experimental studies showed that mulberry leaf supplementation could delay cataract progression in an alloxan-induced model by decreasing lens lipid peroxidation and enhancing enzyme activities (Andallu & Varadacharyulu, 2002). The polyphenols and flavonoids found in mulberry leaves can mitigate these effects by scavenging free radicals, maintaining the structural integrity of lens proteins, and protecting lens epithelial cells from oxidative injury and apoptosis. These protective actions keep the lens transparent and minimize the risk of visual impairment associated with diabetes-related cataracts.

9 EXPERIMENTAL AND CLINICAL EVIDENCE

Mulberry leaf extracts contain bioactive compounds, such as flavonoids, alkaloids, polyphenols, and polysaccharides, and exhibit anti-hyperglycaemic, anti-oxidative, anti-inflammatory and antihyperlipidemic activities. Through inhibiting α-glucosidase, they act on glucose metabolism regulation, insulin sensitivity enhancement, oxidative stress reduction, and inflammation modulation (Tiwari & Rao 2002; Kimura et al. 2007). They also enhance antioxidant enzyme activity, reduce lipid peroxidation, and protect pancreatic β-cells. In animal models of diabetes, mulberry leaves lower fasting and postprandial glucose, HbA1c, and serum lipids as well as improved glucose tolerance and insulin sensitivity (Zhang et al., 2025). They increase antioxidant enzymes like SOD, CAT, GPx and GST that decrease the oxidative damage. Molecular studies link this to AMPK activation, upregulation of Nrf2 antioxidant pathways, FFA-induced NF-κB suppression, and enhanced mitochondrial function (Cheng et al., 2024). Mulberry polyphenols inhibit

advanced glycation end product (AGE) formation, reduce inflammatory cytokines, and improve endothelial function, protecting against diabetic nephropathy, neuropathy, retinopathy, and cardiovascular diseases.

Clinical studies in diabetic and prediabetic individuals have validated that mulberry preparations improve postprandial glucose and insulin sensitivity without serious adverse events (Kimura et al. 2007). They also enhance lipid levels, markers of oxidative stress and inflammation, and body weight. Phytonutrient studies suggest that mulberry extracts promote a diverse gut microbiota and elevate short-chain fatty acid levels, resulting in decreased metabolic imbalance as well as inflammatory balance associated with insulin resistance and obesity (Cheng et al., 2024). 2 A possible role in ameliorating this is mulberry leaves, which are cheap to produce and high in bioactivity for safety and multitarget effects. However, large randomised trials are needed to confirm dosages, pharmacokinetics, safety, and efficacy.

Safety Toxicity and Limitations

Studies have reported low toxicity and fair-to-good tolerability of mulberry leaf products with moderate consumption (Kimura et al., 2007). They have antihyperglycemic, antioxidant, anti-inflammatory, antihyperlipidemic, and cytoprotective benefits without causing severe hypoglycemia or the major side effects associated with synthetic antidiabetic agents. However, excessive consumption can cause gastrointestinal discomfort (bloating and diarrhea) due to the presence of 1-deoxynojirimycin (DNJ), which slows down carbohydrate digestion. Using mulberry with antidiabetic medications may increase the risk of hypoglycaemia; therefore, monitor blood glucose levels. Phytochemical content and consistency of therapeutic action depend on variations in species, cultivation, harvest, and processing.

Major knowledge gaps include the need for large-scale, long-term clinical trials on efficacy, population pharmacokinetics, dosage, and safety. Such variability in the concentration of bioactive compounds (e.g., flavonoids, polyphenols, and 1-deoxynojirimycin (DNJ)) makes standardization difficult. The therapeutic applications of mulberry leaves for the safe and effective management of diabetes require further exploration through toxicology, clinical trials, metabolomics, and pharmacological standardization.

10 FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Mulberry (Morus spp.) exhibits extensive antidiabetic and antioxidant potential, as supported by the existing evidence. However, its widespread implementation for diabetes management and prevention of complications deserves further investigations. Given that the available studies of efficacy, safety, pharmacokinetics and dosage are predominantly limited to animal models or short human trials, further assessments in large-scale randomized clinical trials through heterogeneous populations will be required. Detailed molecular characterization is necessary to elucidate the multi-target mechanisms of action of mulberry phytochemicals modulating AMPK, Nrf2, NF-κB, and AGE-RAGE signalling, as well as mitochondrial biogenesis and gut microbiota, with the application of integrated omics approaches for in-depth insights. Standardization of cultivation, extraction, and quality control is also another area of importance. The modulatory effect of mulberry on gut microbiota raises the possibility that it may assist in combating obesity, insulin resistance, inflammation, and diabetes (especially type-2 DM), even though its clinical efficacy is still unclear but might be useful against cardiovascular diseases, neurodegenerative diseases, obesity-related fatty liver disease, as well as aging-related oxidative stress. The full therapeutic potential of mulberry leaves to make diabetes care safer and more affordable can only be realised through multidisciplinary research.

11 CONCLUSION

Diabetes mellitus is one of the common metabolic disorders associated with oxidative stress, inflammation, mitochondrial dysfunction, and metabolic imbalance that can ultimately cause various complications, including kidney, nerve, retina and cardiovascular damage. Chronic hyperglycaemia promotes reactive oxygen species (ROS) generation through glucose auto-oxidation, mitochondrial electron leakage, advanced glycation end products, and inflammatory mediators. Overproduction of ROS leads to lipid peroxidation, protein oxidation and DNA damage, endothelial dysfunction and apoptosis which may all accelerate the complications of diabetes. Mulberry (Morus spp.) leaves are rich in many bioactive components, such as flavonoids, alkaloids, polyphenols, polysaccharides, vitamins, and minerals, with strong antioxidant effects, as well as anti-hyperglycaemic, anti-inflammatory, and cytoprotective effects. Supplementation of mulberry leaf decreased blood glucose levels by regulating insulin sensitivity and enhancing antioxidant enzyme activities as well as anti-inflammatory effects; concurrently, α-glucosidase inhibition action is postponed at the early stage, thereby improving diabetic complications. Mulberry phytochemicals modulate AMPK, Nrf2, NF-κB and AGE-RAGE pathways and improve mitochondrial function and gut microbiota.

Mulberry leaves have great potential as functional foods, nutraceuticals, and adjunct therapies for diabetes due to their therapeutic effects, nutritional benefits, safety, and traditional use. But it requires extensive clinical trials, standardization of dosage, and long-term safety studies. Future research in related disciplines such as molecular

biology, pharmacology, biotechnology, and nutrition may further explore the use of these micronutrients to combat diabetes and oxidative stress-related disorders. Thus, mulberry leaves provide a natural way to manage oxidative stress and delay diabetes complications while enhancing metabolic health and, in turn, quality of life.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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The authors declare no conflicts of interest regarding this manuscript.

Declaration of AI Use

The author acknowledges using Grammarly and ChatGPT to assist with grammar checking, language refinement, and reference formatting. The author did not use these AI-assisted tools to replace their intellectual contributions or scholarly judgment. All AI-assisted outputs, including content, references, and interpretations, were carefully reviewed, revised, verified, and approved by the author. The author accepts full responsibility for the accuracy, integrity, and final content of the manuscript.

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