

Relevance of mango use in patients with 2 type diabetes mellitus

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Mango fruits and mango leaf extracts (*Mangifera indica*) are a medicinal plant used to treat diabetes and its complications. The tender leaves of the mango tree contain tannins called anthocyanidins, which help treat early diabetes. The leaves contain the compound 3-beta-taraxerol and ethyl acetate extract, which interacts with insulin, activating GLUT4 and stimulating glycogen synthesis. Mango leaves have powerful antioxidant properties because they contain a large amount of flavonoids, phenols, zeaxanthin and beta-carotene. Animal studies have shown that mangiferin can counteract the free radical associated with cancer, diabetes, and other diseases.

Keywords: *Diabetes mellitus, Mangifera indica, flavanoids, treatment.*

Актуальність застосування манго у пацієнтів із цукровим діабетом 2-го типу

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Плоды манго та екстракти листків манго (*Mangifera indica*) є лікарським засобом, який використовують для лікування діабету і його ускладнень. Листки мангового дерева містять дубильні речовини, які називають антоціанідинами. Вони допомагають лікувати ранній діабет. Листки містять 3-бета-тараксерол і етилацетатний екстракт, який взаємодіє з інсуліном, активує GLUT4 та стимулює синтез глікогену. Листки манго мають потужний антиоксидантний потенціал, містять велику кількість флавоноїдів, фенолів, зеаксантину та бета-каротин. Дослідження на тваринах продемонстрували, що мангіферин може протидіяти пошкодженню клітин вільними радикалами та пов'язаними з цим захворюваннями, такими, як рак, цукровий діабет.

Ключові слова: *цукровий діабет, Mangifera indica, флавоноїди, лікування.*

Актуальность применения манго у пациентов с сахарным диабетом 2-го типа

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Плоды манго и экстракты листьев манго (*Mangifera indica*) являются лекарственным растением, используемым для лечения диабета и его осложнений. Листья мангового дерева содержат дубильные вещества, называемые антоцианидинами, которые помогают лечить ранний диабет. Листья манго содержат соединение 3-бета-тараксерол и этилацетатный экстракт, который взаимодействует с инсулином, активируя GLUT4 и стимулируя синтез гликогена. Кроме того, листья манго обладают мощными антиоксидантными свойствами, поскольку содержат большое количество флавоноидов, фенолов, зеаксантины и бета-каротин. Исследования на животных продемонстрировали, что мангиферин может противодействовать свободнорадикальному повреждению клеток и связанными с этим заболеваниями, такими, как рак, сахарный диабет.

Ключевые слова: *сахарный диабет, Mangifera indica, флавоноиды, лечение.*

Mangiferin has a therapeutic potential against lifestyle disorders. Mangiferin (2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanten-9-one) can be isolated from higher plants, as well as from the fruits of mangoes and other parts of the plant (i.e. peel, seed and kernel). It has a number of health-supporting properties, such as antioxidant, antimicrobial, antidiabetic, antiallergic, antitumor, hypocholesterolemic and immunomodulating. It inhibits the activation of peroxisome proliferator activated isoforms by altering the transcription process. Mangiferin protects against various types of cancer, including lung and colon cancer, by suppressing the expression of tumor necrosis factor α, the inducible potential of nitric oxide synthase, and the proliferation and induction of apoptosis [3, 17].

Mangiferin protects against cancer of the nervous system and breast cancer by inhibiting the expression of matrix metalloproteinase (MMP)-9 and MMP-7 and inhibiting the enzymatic activity, metastatic potential and activation of the β-catenin pathway. Mangiferin is able to block lipid peroxidation, enhances the activity of the macrophage monocyte system and has an antibacterial effect against gram-positive and gram-negative bacteria. The current review article is an attempt to explain the therapeutic potential of mangiferin, a bioactive compound of the mango, against lifestyle-related disorders. Mangiferin (2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one) can be isolated from higher plants as well as the mango fruit and their

byproducts (i.e. peel, seed, and kernel). It possesses several health endorsing properties such as antioxidant, antimicrobial, antidiabetic, antiallergic, anticancer, hypocholesterolemic, and immunomodulatory. It suppresses the activation of peroxisome proliferator activated receptor isoforms by changing the transcription process [4, 6, 13, 16].

Mangiferin protects against different human cancers, including lung, colon, breast, and neuronal cancers, through the suppression of tumor necrosis factor expression, inducible nitric oxide synthase potential, and proliferation and induction of apoptosis. It also protects against neural and breast cancers by suppressing the expression of matrix MMP-9 and MMP-7 and inhibiting enzymatic activity, metastatic potential, and activation of the β-catenin pathway. It has the capacity to block lipid peroxidation, in order to provide a shielding effect against physiological threats. Additionally, mangiferin enhances the capacity of the monocyte-macrophage system and possesses antibacterial activity against gram-positive and gram-negative bacteria. This review summarizes the literature pertaining to mangiferin and its associated health claims [1, 10].

The research data showed that Mangiferin plays a pro-hypoglycemic role by modulating glucose metabolism, improving insulin resistance, lowering cholesterol synthesis and suppressing the expression of tumor necrosis factor α and inducible nitric oxide synthase. It also induces apoptosis and inhibits the pro-

gression and stimulation of cell proliferation, interfering with the regulation of the cell cycle, signaling several pathways of cancer transduction in tumor cells [5].

Mangiferin is obtained from mango with many other active ingredients, but with poor lipophilicity and hydrophilicity. Mangiferin concentrations were measured by High performance liquid chromatography (RP-HPLC) in rats administered orally with crude mangiferin and the mangiferin-phospholipid complex. The results showed that the solubility of the mangiferin-phospholipid complex in water and n-octanol was improved, and the oil-water complex distribution coefficient improved 6.2 times. In addition, rats showed a significant improvement in intestinal permeability. AUC and peak plasma concentration in rats treated with untreated mangiferin were lower than those treated with mangiferin-phospholipid complex. In the experiment, when the mangiferin complex was administered to rats that received carbon tetrachloride, hepatoprotective property was revealed by restoring hepatic antioxidants and serum hepatic enzymes [11, 15, 16].

The bioavailability of mangiferin in rats increased by 9.75 times when using the mangiferin complex compared to pure mangiferin. In addition, hepatoprotection in rats was increased by administration of the mangiferin-soy phospholipid complex due to improved bioavailability. Zhang et al. It was determined that the recovery of mangiferin in the eye ranged from 80.0 to 85.6%, and in plasma from 82.0 to 88.0% [8]. Mangiferin can pass through the blood-brain barrier and it is proved that it is effective in reducing the treatment time for various eye diseases. Similarly, the concentration of mangiferin in plasma (from 0.6 to 24 µg/ml) and urine (from 0.48 to 24 µg/ml) was studied using HPLC [9].

Eight weeks of mangiferin treatment significantly lowered plasma glucose and triglyceride (TG) levels in db/db mice. It enhanced pancreatic β-cell mass and amount of glucose and insulin uptake along with increased the phosphorylation of AMP-activated protein kinase (AMPK) in n 3 T3-L1 cells. It also activated the AMP-activated protein kinase (AMPK) phosphorylation of AMPK and activated along its downstream target, acetyl -CoA carboxylase (ACC) in the liver, hypothalamus, muscle and adipose tissue of C57BL/6 mice. Likewise, the oral administration of mangiferin (20 mg/kg, intraperitoneal administration (i.p.)) for 4 weeks in streptozotocin-induced hyperglycemic rats improved insulin sensitivity, modulated lipid profile, and reverted adipokine levels. Similarly, different concentrations of mangiferin (15, 30, and 60 mg/kg/day oral administration) were given to diabetic rats for 9 weeks, resulting in a reduction of osteopontin production, kidney inflammation, and renal fibrosis. Chronic treatment with mangiferin prevented renal glomeruli fibrosis, as well

as decreased α-smooth muscle actin and collagen IV expression in the diabetic rat. In contrast, this also reduced the expression of osteopontin in the renal-cortex of diabetic rats, COX-2 and NF-κB P65 subunits. Finally, mangiferin reduced interleukin-1β in the serum and kidneys of diabetic rats [12].

Mangiferin has also been shown to lower ROS production and decrease intracellular antioxidant defenses, and mediates diabetic nephropathy, as it modulates the MAPK (P38, JNK and ERK1/2), PKC isoforms (PKCα, PKCβ and PKCε), TGF-β1 pathways, as well as the NF-κB signaling cascades involved in this pathophysiology Wang et al. determined that mangiferin exhibited an antidiabetic role in adult C57BL/6 J mice. The administration of mangiferin (30 and 90 mg/kg BW) improved glucose tolerance and glycemia, increased β-cell hyperplasia and serum insulin levels, lowered β-cell apoptosis, elevated β-cell proliferation and upregulated cyclin D1, D2 and cyclin-dependent kinase 4 (Cdk4) at 7–14 days post-partial pancreatectomy. Additionally, mangiferin promoted β-cell regeneration and the expression of pancreatic and duodenal homeobox gene 1 (PDX-1), glucose transporter 2 (GLUT-2), neurogenin 3 (Ngn3), glucokinase (GCK), and Forkhead box protein O1 (Foxo-1) [2].

Mangiferin (15, 30 and 60 mg/kg) treatment for nine weeks significantly improved chronic renal insufficiency of diabetic rats, and was demonstrated to reduce kidney weight index, albuminuria, glomerular extracellular matrix expansion, blood urea nitrogen, and glomerular and accumulation basement membrane thickness. Meanwhile, it also enhanced the enzymatic activity, as well as the protein and mRNA expression of Glo-1, as well as decreased the mRNA and protein expression of advanced glycation endproducts (AGEs) and receptor for advanced glycation end products (RAGE) receptor in diabetic rat renal cortex. Moreover, it also reduced the concentrations of malondialdehyde (MDA) and enhanced the concentrations of glutathione in the diabetic rat kidney [18].

Mangiferin (10 and 20 mg/kg) administered once daily for 28 days in STZ-induced diabetic rats exhibited anti-diabetic activity. It significantly reduced plasma low-density lipoprotein cholesterol (LDL-C) and TG levels, lowered total cholesterol level and increased high-density HDL-C levels. Furthermore, the atherogenic index of diabetic rats decreased and mangiferin improved oral-glucose tolerance in normal rats loaded with glucose [7].

In diabetic nephropathy rats, mangiferin considerably lowered the serum levels of advanced glycation end products, red blood cell sorbitol concentrations, malonaldehyde level, 24 h albuminuria excretion, and enhanced serum antioxidant enzymes

Health perspectives of Mangiferin in the treatment of diabetes mellitus 2

Diabetes prevention	Increased glucose and pancreatic beta cell mass Activation of phosphorylation of AMP-activated protein kinase
	Increasing insulin sensitivity, correcting the lipid profile and normalizing adipokine levels
	TGF-β1 pathways, PKC isoforms (PKCα, PKCβ and PKCε), MAPK (P38, JNK and ERK1/2) modulated
	β-cell apoptosis reduction Activate cyclin D1, cyclin D2 and Cdk4 (cyclin-dependent kinase 4), which promotes β-cell regeneration and expression of the duodenal and pancreatic homeobox gene 1 (PDX-1), glucose transporter 2 (GLUT-2), neurogenin 3 (Ngn3) , glucokinase (GCK) and Forkhead box protein O1 (Foxo-1)
	The expression of Glo-1 mRNA is enhanced, the activity of protein and enzymes is increased Decreased expression of mRNA and protein receptors in glycation end products and in glycosylation end products
	Reducing the concentration of red blood cells, sorbitol, the level of malonaldehyde Inhibition of expansion of the glomerular extracellular matrix, accumulation and transformation of overexpression of growth factor beta 1
	Prevention of renal glomerular fibrosis Decreased expression of alpha smooth muscle of collagen IV and actin Decreased expression of COX-2, NF-κB p65 and osteopontin subunit Decrease in interleukin-1β

such as superoxide dismutase and glutathione peroxidase. In addition, it inhibits the expansion of glomerular extracellular-matrix and diabetic nephropathy rat glomeruli TGF- β 1 accumulation and transformation, high glucose-induced mesangial cell proliferation and mesangial cells collagen IV in a glomerular diabetic nephropathy rat model [12].

Mangifera indica leaf extract induce production of Adiponectin in the adipose tissue and leptin production both in adipose tissue and small intestine. This increases the glucose uptake in the muscle and liver. Adiponectin and leptin increase improve the action of Glut-4 in liver and muscles. It improves glucose metabolism and adipogenesis [6].

Adiponectin prevents insulin resistance, it exerts insulin-sensitizing effect through binding to its receptors, leading to activation of AMPK, PPAR- α , and potentially other unknown molecular pathways. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are downregulated, leading to activation of a signaling pathways involved in metabolism regulation. Up-regulation of adiponectin/adiponectin receptors or enhancing adiponectin receptor function may be an interesting therapeutic strategy for obesity-linked insulin resistance and diabetes mellitus type 2 [14, 19].

The health perspectives of Mangiferin indica in treatment of diabetes mellitus 2 is shown in Table.

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