

MANGIFERIN: A POTENTIAL NATURAL MOLECULE FOR MANAGEMENT OF METABOLIC SYNDROME

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ABSTRACT

The incidence of metabolic syndrome is rising at an unprecedented pace. The technological advancements, lifestyle changes and mechanization are all considered responsible for this rising global health issue. Nature-derived phytochemicals possess several unique properties that may be useful for management of metabolic syndrome. Mangiferin, present in various plant species, has been shown to have anti-obesity, anti-diabetic, anti-oxidant and anti-inflammatory properties. Mangiferin also modulates glucose and lipid metabolisms and restores glucose and lipid homeostasis.

In this review, we attempt to provide the latest information available on mangiferin and its effects on various biological processes associated/implicated in metabolic syndrome.

Keywords: Mangiferin, Metabolic syndrome, Obesity, Type 2 diabetes, Inflammation, Oxidative stress.

INTRODUCTION

Metabolic syndrome is a constellation of closely associated disorders whose common root cause is the sedentary lifestyle, intake of calorie-rich diet, reduced physical activity sleep deprivation and stress. This group of symptoms comprises of obesity, type 2 diabetes mellitus, insulin resistance and hyperglycemia, hypertension, non-alcoholic fatty liver disorder, cardiovascular disorders and dyslipidemia [1]. One of the principal causes behind metabolic syndrome is obesity. The obesity epidemic represents a serious public health concern due to its increasing incidence and associated risk profile for several diseases and consequent morbidity and mortality. A recent report by the WHO states that globally 39% of adults aged 18 and over, were overweight in 2014, and 13% were falling under the obese category [2].

Natural compounds and herbs have been traditionally used to treat and cure various disorders associated with imbalanced metabolism. Based on the fact that plants have been used to manage human health for more than 3000 y, and that they are easily available to local populations, use of plant derived herbal products for the management of obesity, and diabetes is an attractive and promising area of research. Ancient Ayurvedic texts describe several herbs and herbal extracts for treatment of obesity and associated metabolic syndrome. Various studies have described the benefits of using plant extracts for treatment of obesity, insulin resistance, type 2 diabetes, and polycystic ovary syndrome in obese individuals [3-6].

In the present review, we summarize the therapeutic potential of one such molecule, mangiferin, for treatment of metabolic syndrome as it modulates several biological processes related to energy generation, energy expenditure and metabolism.

Chemical properties and occurrence of mangiferin

Mangiferin is a naturally-occurring polyphenol of C-glycosylxanthone structure with diverse pharmacological actions. Mangiferin is widely present in higher plants. It is present in higher concentration in *Mangifera indica*, *Cyclopia* and *Salacia* species. Mangiferin has been reported to possess analgesic, anti-diabetic, anti-sclerotic, antimicrobial, antiviral, cardio-, hepato-, and neuro-protective, anti-inflammatory and anti-allergic properties. It is sold for treatment of metabolic disorder in Cuba under the trade name of Vimang [7, 8]. The presence of catechol moiety containing four hydroxyl groups makes mangiferin an efficient anti-oxidant and anti-free radical molecule [8, 9]. Mangiferin is poorly soluble in aqueous solutions. Solubility and intestinal permeability of

mangiferin is found to be increased through its complexation with phospholipids enhancing the bioavailability by 2.3 times compared with crude mangiferin in experimental rats [10]. Complexation of mangiferin with β -cyclodextrin also improves thermal stability and water solubility of mangiferin revealing the potential usefulness of mangiferin derivatives in preparation of novel thermally stable formulations [11].

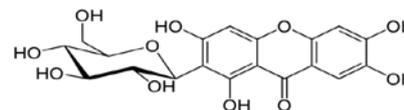


Fig. 1: Structure of mangiferin

Mangiferin ameliorates obesity and associated metabolic syndrome

Onset of metabolic syndrome disrupts the homeostatic balance between various organs such as the liver, pancreas, heart, brain, adipose tissue and various other regulatory cells throughout the body [1]. Herbal extracts of *Mangifera indica* whose principle component is mangiferin have been shown to counteract obesity/metabolic syndrome. It has been demonstrated that 1% mango seed kernel extract in hot water (MESK-W) prevented weight gain and liver steatohepatitis in high fat diet treated mice [12]. Kobayashi *et al.* have shown that in 3T3-L1 adipocytes, 1% MESK-W inhibited cellular lipid deposition by reducing glycerol 2-phosphate dehydrogenase activity and PPAR γ and C/EBP α expression levels [12]. Moreno *et al.* have shown that ethanolic extract of *Mangifera indica* from both stem bark and leaves inhibit the action of pancreatic lipase, and lipoprotein lipase, reduce fat absorption and increase fecal fat excretion. Moreover, *Mangifera indica* extract down-regulated the expression of several genes associated with the pathophysiology of obesity and inflammation such as lipoprotein lipase, hormone-sensitive lipase, fatty acid synthase and resistin in liver and epididymal fat [13]. Moreover, it was found to decrease the expression DGAT2, SREBP-1c, ACC genes, and up-regulated CD36, PPAR- α , CPT-1 expression and prevented fat deposition in visceral fat pad and liver [14, 15]. Similar studies in our lab have proven that ethanolic extract of *Mangifera indica* seed kernel prevented weight gain in diet-induced obese mice, which was comparable with standard anti-obesity drug Orlistat [16]. The inflammatory response

by the body is generally helpful in removing viruses, bacteria and other pathogens and is a crucial element of the innate immune system. Increased number of white blood cells, higher plasma concentrations of pro-inflammatory markers like TNF- α , certain interleukins, IFN- γ , C-reactive protein, adhesion molecules and E and P selectins are indicators of systemic inflammation. Moreover, higher insulin and decreased leptin and adiponectin levels are also considered markers of inflammation [17]. It has been shown by several investigators that “chronic-low grade inflammation” triggers metabolic syndrome and this continuing systemic inflammatory milieu upsets the delicately balanced intricate metabolic pathways. In obesity, this inflammatory state becomes “chronic” due to the consistent release of pro-inflammatory cytokines, whose major source is classically activated macrophages (M1 phenotype) present in inflated adipose tissue [18].

As inflammation and ensuing oxidative stress forms a critical part of metabolic syndrome, reducing pro-inflammatory milieu holds a promising strategy to manage metabolic syndrome. Pro-inflammatory cytokines such as IL-1 impair insulin signaling by reducing the expression of Insulin Receptor Substrate-1 (IRS-1) and markedly inhibiting GLUT-4 translocation to the plasma membrane [19]. TNF- α is an adipokine having potent inflammatory activity. It is over-expressed in obesity and considered to be one critical factor involved in progression of obesity associated diabetes mellitus [20]. The anti-inflammatory activity of mangiferin is attributed to its inhibitory action on potent inflammatory pathway NF- κ B and pro-inflammatory cytokines Interleukin-1 and TNF- α [21].

Inducible-nitric-oxide synthase (iNOS) plays a major role in obesity-induced insulin resistance. Shinozaki *et al.* have demonstrated that over-expression of iNOS in the liver induces hepatic insulin resistance in experimental mice [22]. It has been shown that mangiferin decreased the mRNA levels of iNOS, TNF- α and increased the expression of TGF- β . Moreover, it also reduced levels of (iNOS) and cyclooxygenase-2, which are required in the synthesis of inflammatory mediators [23]. These findings suggest that mangiferin can be a valuable tool for the treatment of inflammation, cancer, autoimmune disorders, atherosclerosis and coronary heart disease [24]. Mangiferin can be used to treat sepsis as it inhibits pro-inflammatory NF- κ B pathway and up regulates heme oxygenase-1 expression in the lungs [25]. Mangiferin treatment in Wistar rats reduced neuro-inflammation and brain oxidative damage by reducing glucocorticoids, IL-1 β , NF- κ B, TNF- α , and its receptor TNF-R1 levels in plasma. Bhatia *et al.* have demonstrated that in microglial cells mangiferin inhibits LPS induced synthesis of prostaglandin E2 and COX-2, and reduced the pro-inflammatory milieu in the brain. However, mangiferin did not affect the expression of iNOS and TNF- α in activated microglial cells. Taken together, mangiferin reduces cerebral damage owing to its potent anti-inflammatory and anti-oxidant properties [26]. In murine activated macrophages mangiferin inhibited the expression of *RelA/RelB* thus preventing the activation of NF- κ B signaling cascade. Additionally, it inhibited a large array of genes, which are crucial in regulation of apoptosis, inflammation and body homeostasis (fig. 3) [21].

Mangiferin ameliorates oxidative stress

Generation of reactive oxygen species leads to cellular membrane damage and is implicated in the pathology of obesity, diabetes, atherosclerosis and cardiovascular disorders. Obesity is characterized by systemic increase in reactive oxygen species levels, which are known to reduce insulin sensitivity [27]. Mangiferin has been shown to possess higher free radical scavenging capacity, and the ferric reducing ability of plasma (FRAP) compared with other anti-oxidants such as L-ascorbic acid and Trolox, a vitamin E analog. Human Umbilical Vein Endothelial Cells (HUVEC) treated with mangiferin showed significantly higher survival under hydrogen peroxide induced oxidative stress [28].

Elevated levels of free radicals and reactive oxygen species promote development of various pathophysiological conditions associated with diabetes mellitus. Diabetics have been reported to suffer with heightened oxidative stress due to increased activity of polyol and hexosamine pathways, higher advanced glycation end product and increased expression of AGE receptors [29]. Diabetics have been

found to have higher oxidation of plasma proteins and reduced free radical scavenging ability compared to healthy controls [30]. Diabetes is also characterized by decreased activities of anti-oxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) and increased malondialdehyde, advanced oxidation protein products and protein carbonyls [31]. In a rat model for galactosamine induced hepatic pathophysiology mangiferin exerted hepatoprotective activity by reducing oxidative stress and consequent cellular damage by inhibiting NF- κ B pathway and enhancing cellular anti-oxidant defense via the Nrf-2 pathway [32]. Oral administration of mangiferin in STZ induced diabetic rats decreased blood glucose and increased plasma insulin levels [33]. It has been observed that mangiferin administration significantly increased the levels SOD, CAT and glutathione peroxidase and treatment with mangiferin also prevents cellular membrane damage by reducing lipid peroxidation [33].

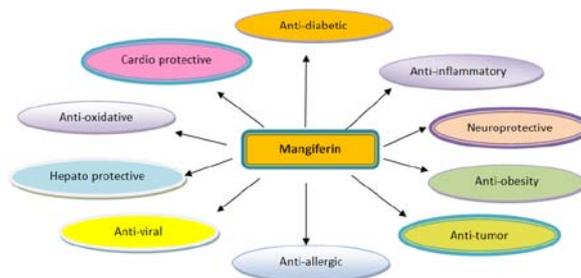


Fig. 2: Therapeutic effects of mangiferin

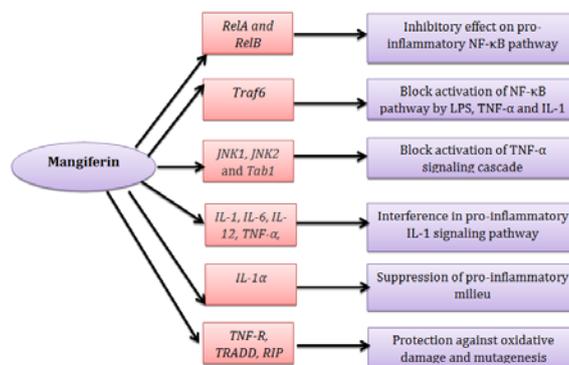


Fig. 3: Inhibition of inflammatory genes by mangiferin [21]

Mangiferin in treatment of diabetes

Diabetes is characterized by hyperglycemia, defects in cellular uptake of glucose due to decreased insulin sensitivity and increased gluconeogenesis in the liver. Hyperglycemia in diabetics is attributed to decreased insulin sensitivity in insulin target organs like muscles, liver and adipose tissue. Improper utilization of glucose in key glucose utilizing pathway leads to hyperglycemia. Other key mechanisms contributing to hyperglycemia is higher hepatic out-put of glucose due to increased activity of gluconeogenesis pathway.

Mangiferin promotes glucose utilization by increasing its cellular uptake. It has been shown that *Salacia oblonga* extract, whose main active component is mangiferin, increased glucose uptake by 50% in rat myotubes and 3T3-L1 adipocytes. At 1 mM, mangiferin increased glucose utilization by two folds in 3T3-L1 cell lines compared to untreated controls [34]. The increased cellular uptake of glucose is attributed to the enhanced surface expression of GLUT4 transporters [35]. In a dose-dependent manner mangiferin down-regulates the expression of key gluconeogenesis pathway enzyme namely fructose-1,6-bisphosphatase (FBP). Inhibition of gluconeogenesis in the liver reduces hepatic glucose production and thus reduces blood-glucose levels [36].

Puriyari *et al.* have demonstrated that in STZ-induced diabetic mice mangiferin treatment increased the activity of glycolytic and

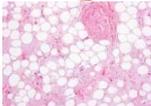
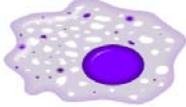
glycogen synthesis pathways, while decreased gluconeogenesis [37]. Ethanol extract of *Mangifera indica* has been shown to inhibit α -glucosidase activity *in vitro* making mangiferin a potential treatment agent against obesity and diabetes [38]. Complex carbohydrate molecules are broken down into glucose in the gut by a glucosidase class of enzymes such as sucrase, isomaltase and maltase. Mangiferin has also been shown to reduce glucose absorption through its inhibitory effect on α -glucosidase enzymes in experimental rats. This extra pancreatic action of mangiferin reduces glucose absorption and subsequent rise in blood-glucose levels [39]. It has been established that mangiferin derivatives inhibit protein tyrosine phosphatase1B (PTP1B) activity and PTP1B inhibition is considered to be a potential target for treatment of diabetes mellitus [40].

It has been shown that 40 mg/kg body weight mangiferin is anti-hyperglycemic in STZ induced diabetic rats by enhancing insulin secretion and activities of key enzymes of carbohydrate metabolism [41]. This dose reduced pancreatic β -cell damage, regenerated insulin secreting β -cells, and improved non-enzymatic, anti-oxidant

status in STZ induced diabetic mouse thus protecting the mouse against diabetes [42]. At the same dose mangiferin treatment significantly reduced several other parameters such as blood glucose, urea, uric acid, creatinine and enzymes like AST, ALT and ALP in STZ induced diabetic rats [43].

Chronic treatment with mangiferin significantly ameliorated renal dysfunction in diabetic rats, as evidenced by a decrease in kidney damage markers like albuminuria and blood urea nitrogen. Moreover, mangiferin treatment caused substantial increases in glyoxysylase-1 enzymatic activity, glutathione levels and reduced the levels of advanced glycation end products, lowered lipid peroxidation and reduced malondialdehyde in the kidney of diabetic rats [44]. Methanolic extracts of *Mangifera indica* reduced the levels of glycated hemoglobin by 20.78% and 27.33% after 14 and 21 d treatment respectively compared with non-treated animals [45]. Esterified-derivatives of mangiferin have proven to be potent hypoglycemic molecules as compared to mangiferin itself. The lipid solubility and islet protective effects of esterified-derivatives were also found to be stronger than crude mangiferin [46].

Table 1: Physiological effect of mangiferin on effector organs (1) Liver (2) Brain (3) Intestine (4) Adipose (5) Pancreas (6) Macrophages and (7) Kidney

S. No.	Effector Organ	Action	References
1		↓ Liver steatohepatitis ↓ Nrf-2 ↑ SOD, CAT, glutathione peroxidase ↓ NF- κ B ↓ Lipid peroxidation ↓ Gluconeogenesis	[12],[32],[33],[36]
2		↓ NF- κ B ↓ TNF- α ↓ iNOS	[26]
3		↓ Fat absorption ↑ Fecal fat excretion ↓ Glucose absorption ↓ α -glucosidase activity	[13],[38]
4		↓ Weight gain ↑ GLUT4 activity ↑ Glucose utilization ↑ Insulin sensitivity	[16],[35]
5		↓ Pancreatic lipase action ↓ Lipoprotein lipase action ↓ β -cell damage	[13],[42]
6		↑ TGF- β ↓ RelA/RelB ↓ Cyclooxygenase-2 ↓ Interleukin-1	[21]
7		↑ Glyoxysylase-1 activity ↓ Albuminuria ↓ Blood urea nitrogen ↓ Glutathione ↓ Advanced glycation end products	[44]

Concluding remarks

In summary, natural compounds and herbs, parts of Indian traditional knowledge have been consistently used by humans for treatment of various health conditions. Ancient knowledge and modern science can be combined to produce novel drug molecules for treatment of metabolic disorders. Mangiferin, isolated from various plants, is one such bioactive compound, which has been found to modulate various pathways and processes associated with metabolism, oxidative stress and inflammation. It reduces inflammation by inhibiting synthesis of key inflammatory cytokines and reduces oxidative stress by strengthening the anti-oxidant capacity of the body. Mangiferin is a potent anti-hypoglycemic molecule as it inhibits absorption of glucose from the gut, promotes cellular glucose uptake, enhances the activity of glycolytic enzymes and inhibits gluconeogenesis. Mangiferin also

reduces damage to kidneys, liver and could be a potential lead molecule for further development as a potent anti-obesity, anti-diabetic and anti-inflammatory molecule.

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CONFLICT OF INTERESTS

Authors have no conflict of interest.

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