

# Therapeutic Potential of the Natural Product Mangiferin in Metabolic Syndrome

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**Abstract:** Natural products have long been and continue to be attractive source of nutritional and pharmacological therapeutics. Interest in natural compounds as potential therapies for metabolic syndrome have recently focused on hydroxylated aromatics, such as resveratrol. Another compound of interest in this regard is mangiferin, the predominant constituent of extracts of the mango plant *Mangifera indica*. Mangiferin has documented antioxidant, cardioprotective and anti-inflammatory effects. Recently, pilot studies indicate bioactivity of this compound in mediating insulin sensitivity and modulating lipid metabolism. In this review we provide information on what we know about the impact of mangiferin on important biological processes involved in metabolic disorders.

**Keywords:** Mangiferin, metabolism, mitochondrial, oxidative stress, inflammation, hyperlipidemia, hyperglycemia, lipogenesis, lipolysis, gluconeogenesis, glycolysis.

## INTRODUCTION

Metabolic syndrome is a combination of medical conditions including obesity, diabetes, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD) and kidney dysfunctions. Obesity in particular is a major public health issue [1, 2] and it predisposes people to metabolic disorders, such as Type II diabetes, which are now prevalent in the USA and worldwide [3-5]. Metabolic syndrome involves interplay among several organs such as liver, muscle, heart, adipose tissues and pancreas, many types of cells, numerous genes and proteins, and multiple metabolic processes including gluconeogenesis, glycolysis, lipogenesis and lipolysis, all of which are regulated by complex networks and influenced by many factors such as hormones.

Treating and preventing metabolic disorders require modulation of a variety of genes, proteins, cellular signaling pathways and biological processes. Current drug development is slow, and new drugs do not appear quickly enough to halt or reverse these long-term trends in disease. This situation might be due to focus on a drug discovery strategy dominated by finding an activator or inhibitor specifically targeting one protein or gene; i.e. the higher specificity, the more desirable. The approach of high throughput screening of synthetic compounds for modulation of specific targets has not yielded a new wave of pharmacological agents to meet the demands for treating metabolic syndrome, suggesting limitations in this drug discovery

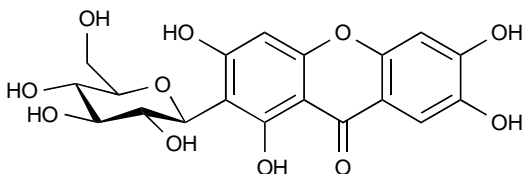
approach [6-8]. Natural compounds, particularly those with histories of medical use, continue to represent an attractive alternative to this approach. Throughout history plants, herbs and fruits have been used as a rich source of medicine. A recent structural comparison between about 10,000 Traditional Chinese Medicine components and about 8,000 modern drugs or candidates identified 908 agent pairs that are structurally similar and 327 agent pairs that are identical in structure [9, 10], indicating an apparent high level of natural products or "natural product-like" representation in modern drugs. These data also suggest to us that potential medicinal applications are still available for known natural products, and the topic of this review is one such compound. The natural compound, mangiferin (MGF), has interesting potential in treatments of metabolic syndromes *via* modulation of multiple biological processes.

## CHEMICAL PROPERTIES AND BIOAVAILABILITY

MGF is widely distributed in higher plants [11]. It is the predominant constituent of *Mangifera indica* extract from the plant that produces mango. In mango plant, MGF abundance is higher in the bark than in other parts of the plant [12]. In mango fruit, MGF content is in the range of 0.3% - 1% (w/w) in peel and less than 1% in flesh [13]. MGF is a C-glucosyl xanthone and chemically named as C2- $\beta$ -d-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone (Figure 1). MGF features a highly condensed aromatic ring system coupled to a glucose moiety *via* an unusual C-C bond. The structure of MGF satisfies Lipinski's rules for druglike properties: molecular weight less than 500, cLogP = 2.73, fewer than 5 donor functions for hydrogen bonds; and fewer than 10 acceptor functions for hydrogen bonds. These structural

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features fulfill the requisites for high bioavailability by oral administration. MGF is rapidly absorbed, for instance in rats, as MGF and its metabolites are detectable in serum and urine of rats within 1 hour after a single dose of oral administration [14, 15]. It has also been shown that MGF is able to traverse the blood-brain barrier in gerbils [16].



**Figure 1:** Chemical structure of mangiferin.

## BIOLOGICAL EFFECTS

### Impact of MGF on Mitochondrial Oxidative Capacity, Oxidant Stress, and Inflammation

Mitochondria are organelles essential for cellular life and normal functions. They generate cellular energy through the tricarboxylic acid (TCA) cycle and the subsequent electron transport chain (ETC). Mitochondrial dysfunction is closely associated with over 50 diseases including metabolic syndromes [17-19]. MGF enhances the activities of those enzymes in the TCA cycle and raises the levels of state 3, state 4 and ATP in mitochondrial respiration [20], an effect consistent with MGF protection of heart from isoproterenol induced myocardial infarction in rats [20]. MGF's ability to enhance mitochondrial respiration also suggests that it can potentially increase energy expenditure and possibly improve catabolism from carbohydrate or fatty acid energy stores.

The mitochondrial respiratory chain is a major source of reactive oxygen species (ROS) within the cell [21-23]. Excessive production of ROS and increased oxidative stress are participants in the development and progression of NAFLD, diabetes and its complications, and CDV [24-29]. Interestingly MGF has well established antioxidant properties, even though it enhances mitochondrial respiration. Structurally, MGF bears a catechol moiety, which enables it to form stable MGF-Fe<sup>2+</sup>/Fe<sup>3+</sup> complexes, preventing Fenton-type reaction and lipid peroxidation [30]. MGF can scavenge ROS [31], thus inhibiting those processes leading to energy charge decrease and protecting against mitochondrial swelling and mitochondrial membrane potential loss [32, 33]. MGF also helps maintain the balance among the enzymes superoxide dismutase, catalase and the glutathione system [34], which have

key roles in the cellular defense system against free radical damage.

ROS derived from mitochondria can act as signal-transducing molecules provoking inflammation [35]. As MGF reduces oxidant stress, presumably it can reduce inflammation. For instance MGF inhibits respiratory burst in rat neutrophils [36]. In addition, MGF suppresses the expression of prostaglandin (PG) endoperoxide synthase 2 and thereby reduces PGE<sub>2</sub> production in rat microglia cells [37]. In primary macrophages from mice, MGF treatment significantly blunts the expression of pro-inflammatory cytokines including IL-1, IL-6, IL-12, TNF $\alpha$  and other cytokines produced by monocytes and macrophages [38]. Over-nutrition triggers inflammation, which in turn contributes to the development of metabolic disorders [39]. Given the intimate relationship between the immune and metabolic systems, it is conceivable that anti-inflammatory effects of MGF could be important factors in contributing to its potential ability to mitigate metabolic syndrome.

### MGF Inhibits Hyperlipidemia and Prevents NAFLD

Physiological fatty acids and lipids are balanced by two processes, lipogenesis and lipolysis. Lipogenesis is catalyzed by acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), elongase, stearoyl-CoA desaturase (SCD), glycerol-3-phosphate acyltransferase (GPAT), and diglyceride acyltransferase (DGAT), which are target genes of sterol regulatory element-binding proteins (SREBPs) [39-43]. Lipolysis is catalyzed by lipase, carnitine palmitoyl transferase 1 (CPT1), long chain acyl-CoA dehydrogenase (LCAD), medium chain acyl-CoA dehydrogenase (MCAD), which are regulated by peroxisome proliferator-activated receptors (PPARs) [44].

Under pathological conditions such as over-nutrition and diabetes, imbalanced fatty acid and lipid metabolism occur, often presenting as accumulation of lipid in plasma, liver and adipose tissues. In some hyperlipidemic animal models including high fat diet (HFD) fed rats and hamsters, MGF was shown to be able to reverse elevated plasma total cholesterol, triglycerides, and LDL caused by HFD and diabetes [45-47]. In livers of HFD fed rats, MGF reduced triglyceride and free fatty acids [46, 47].

Mechanistically, limited literature suggests that MGF reduces ACC and DGAT2 in liver of HFD fed rats or hamsters [46, 47], probably by reducing SREBP-1c

[47]. MGF also increases the ratio of phosphorylated-ACC (p-ACC)/ACC by inducing p-AMPK [46]. Phosphorylated ACC is the inactive form of ACC. AMPK phosphorylates ACC and inhibits ACC activity. In lipolysis, MGF increases CPT1 by inducing PPAR- $\alpha$  [47]. Although more comprehensive studies of the mechanisms of action of MGF are needed to better understand these phenomena, these preliminary reports suggest that MGF suppresses lipogenesis and stimulates lipolysis, thereby preventing HFD induced metabolic syndrome.

### **MGF Reduces Hyperglycemia and Prevents Diabetes**

The hallmark of diabetes is hyperglycemia, a result of overload of carbohydrate, insufficient glucose disposal, and/or over production of glucose. Insufficient glucose disposal can be caused by inadequate insulin, insensitivity to insulin signaling, or impaired carbohydrate utilization mediated by enzymes in glycolysis, pyruvate dehydrogenase or lactate dehydrogenase. Over production of glucose can be caused by abnormally high levels of the enzymes in the gluconeogenesis pathway, such as glucose-6-phosphatase (G6P), fructose-1,6-bisphosphatase (FBP) and glucose-6-phosphate dehydrogenase (G6PDH).

In KK-Ay diabetic mice and STZ induced diabetic rats, MGF has been reported to reduce plasma glucose and insulin levels and increase insulin sensitivity and glucose tolerance [45, 48-50]. It seems that MGF does so *via* several unique mechanisms. MGF is an inhibitor of glucosidase [51], which could enable it to prevent overloaded carbohydrate from being converted to glucose. For the existing glucose, MGF appears to stimulate its utilization. In rat myotubes one of the fractions of *Salacia oblonga* extract, with MGF as the main constituent, increases glucose transporter (GLUT)4 mediated uptake probably *via* activation of AMPK [52]. MGF also induces the enzymes in glycolysis such as hexokinase (HK) and pyruvate kinase (PK), and the enzymes in glycogen synthesis (glycogen, glycogen phosphorylase, glycogen synthase) [50]. Moreover, MGF has been shown to reduce G6P and FBP and therefore inhibits gluconeogenesis [50].

### **MGF Mitigates Cardiac Vascular Diseases**

CVD continues to be the leading cause of death worldwide [3, 4]. Abnormal mitochondrial energy metabolism and oxidative stress are critical to CVD. It

has been shown that MGF can protect heart from isoproterenol induced structural alteration and functional failure in heart of rats [20], probably due to its ability to enhance mitochondrial oxidative capacity and at the same time to reduce ROS.

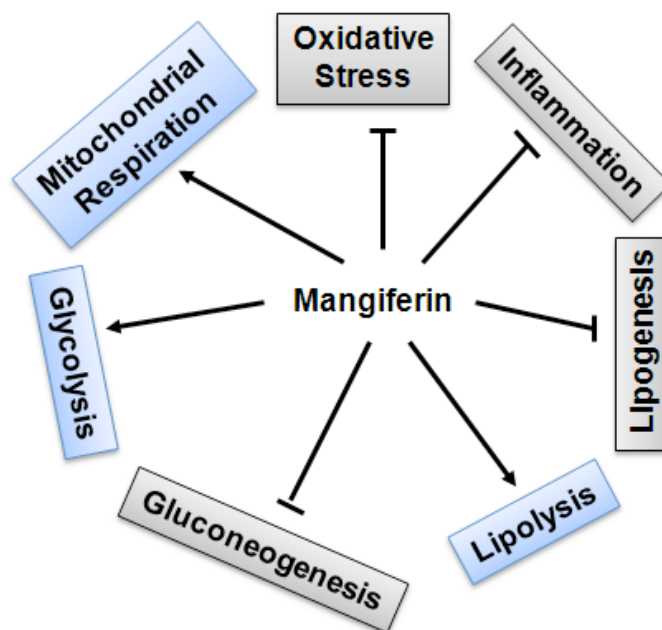
Hyperlipidemia and hyperglycemia are major risk factors contributing to CVD. As MGF is able to mitigate both of these factors, it is conceivable that it can prevent CVD associated with hyperlipidemia and hyperglycemia, although the antihyperlipidemia effects of MGF on CVD are likely to be complicated. As mentioned previously, MGF has the potential to not only suppress lipogenesis but also stimulate lipolysis, part of which is fatty acid oxidation. However, increased cardiac fatty acid oxidation plays a role in the development of myocardial dysfunction in diabetes [53, 54]. For instance cardiac overexpression of PPAR- $\alpha$ , which stimulates  $\beta$ -oxidation, induces pathological cardiac changes [55]. Interestingly, in heart of Zucker diabetic fatty rats (ZDF, a genetic model of type 2 diabetes and obesity), *Salacia oblonga* extracts containing MGF reduced upregulated PPAR- $\alpha$  and CPT-1 and ACO mRNAs, while it enhanced hepatic expression of PPAR- $\alpha$ , CPT-1 and acyl-CoA oxidase (ACO) [53, 56]. These putative tissue specific, perhaps paradoxical, effects of MGF require further verification. Nevertheless, MGF seems to have beneficial effects on improving CVD.

### **TOXICITY**

For any agent to be considered a potential pharmacological or nutritional therapeutics, toxicity is an issue that must be addressed. Limited toxicity studies indicate that MGF is possibly a nontoxic natural compound. In tested rats, there was no lethality or toxic reaction found at doses ranging from 25 – 500 mg/kg of body weight / day for a period of 30 days [50, 57]. Rats treated with MGF at dose as high as 500 mg/kg of body weight / day for 30 days did not show respiratory distress, hair loss, restlessness, convulsions, laxative, coma, weight loss, etc. [50, 57]. Although more studies are necessary to confirm the nontoxic nature of MGF, small amount is probably quite safe to humans, as MGF containing fruit, mango, has been consumed by humans and benefits human health [57-59]. The effects of MGF at higher doses in humans require further investigation.

### **CONCLUSION**

In summary, although very limited and preliminary, the literature thus far shows that MGF interferes with



**Figure 2:** Predicted effects of mangiferin on biological processes involved in metabolic syndrome. MGF stimulates mitochondrial respiration, glycolysis and lipolysis. It suppresses oxidative stress, inflammation, gluconeogenesis and lipogenesis.

multiple biological processes critical to the development of metabolic syndrome (Figure 2). It stimulates mitochondrial respiration, but suppresses oxidative stress and inflammation. These are fundamental processes involved in all metabolic disorders. In addition, MGF enhances glycolysis and inhibits gluconeogenesis and thereby reduces hyperglycemia. It increases lipolysis and suppresses lipogenesis and thereby prevents hyperlipidemia. With more comprehensive and in depth studies, MGF has great potential to be developed into a nutritional/pharmacological therapeutics that could prevent and or reverse metabolic disorders by modulating multiple biological events and processes.

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