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Mangiferin Modulation of Metabolism and Metabolic Syndrome

Ekaterina Vladimirovna Fomenko and **Yuling Chi**

Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA

Abstract

The recent emergence of a worldwide epidemic of metabolic disorders, such as obesity and diabetes, demands effective strategy to develop nutraceuticals or pharmaceuticals to halt this trend. Natural products have long been and continue to be an attractive source of nutritional and pharmacological therapeutics. One such natural product is mangiferin (MGF), the predominant constituent of extracts of the mango plant *Mangifera indica L.* Reports on biological and pharmacological effects of MGF increased exponentially in recent years. MGF has documented antioxidant and anti-inflammatory effects. Recent studies indicate that it modulates multiple biological processes involved in metabolism of carbohydrates and lipids. MGF has been shown to improve metabolic abnormalities and disorders in animal models and humans. This review focuses on the recently reported biological and pharmacological effects of MGF on metabolism and metabolic disorders.

Keywords

Mangiferin; metabolism; inflammation; hyperlipidemia; hyperglycemia

Introduction

The metabolic syndrome has been known as a complex of interwoven risk factors which predispose cardiovascular disease (CVD) and type 2 diabetes mellitus and occur together more likely than alone. According to the most recent Harmonized Definition, metabolic syndrome includes elevated triglyceride (TG) levels and low high-density lipoprotein cholesterol levels, obesity, hyperglycemia and raised blood pressure (1). Obesity and diabetes mellitus remain in high prevalence among all age groups in the USA and worldwide and contribute to the development of metabolic syndrome and a wide range of associated health problems, such as non-alcoholic fatty liver disease (NAFLD) (2–5). Diabetes mellitus and obesity are also major risk factors for development of CVD, which is the leading cause of death worldwide (5).

Metabolic syndrome involves interplay among several organs, including liver, muscles, heart, adipose tissues and pancreas, many types of cells, numerous genes and proteins, and

Correspondence should be addressed to Yuling Chi, Ph.D., Department of Medicine, Ullmann 617, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, Phone: 718 430 8913, Fax: 718 430 8963, yuling.chi@einstein.yu.edu.

Conflict of Interest

Authors have no conflict of interest.

multiple metabolic processes, such as gluconeogenesis, glycolysis, lipogenesis and lipolysis, all of which are regulated by complex networks and influenced by many factors, such as hormones. Insulin resistance (IR) is suggested to be at the core of the syndrome and appears to contribute to multiple processes in the development of metabolic disorders (6).

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 are unlikely to appear quickly enough to halt or reverse these long-term trends in the disease. This situation might be due to a focus on a drug discovery strategy dominated by finding an activator or inhibitor specifically targeting one protein or gene, i.e. the higher the specificity, the more desirable it becomes. 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 (7–9). Some of the existing drugs treating obesity and diabetes have a high risk of side effects on the central nervous and cardiovascular systems. For instance, rosiglitazone was suggested to increase the risk of myocardial infarct or death in recent meta-analyses of randomized trials and retrospective case-control studies when compared to placebo or other therapies for type 2 diabetes (10, 11).

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 (12, 13), indicating an apparent high level of natural products or “natural product-like” representation in modern drugs. Some of these Chinese medicines recently have been proven to ameliorate IR, diabetes and other conditions associated with metabolic syndrome (14–16). These data also suggest that potential medicinal applications are still available for known natural products, and the topic of this review is one such compound, mangiferin (MGF). MGF has interesting potential in treatments of metabolic syndromes via modulation of multiple biological processes.

MGF is wildly distributed in a variety of plants (17). The chief source of MGF is the plant *Mangifera indica* that produces mango (17, 18). MGF exists in the leaves, heartwood and stem bark of mango plant, the latter being the richest source (18). It is also present in the peels and kernels of mango fruit (18). The first study of MGF was reported in 1960. The interest in MGF has gradually increased before the twenty first century and exponentially increased since then, as indicated by the number of publications (Fig. 1). MGF is a C-glucosyl xanthone and chemically named as C2-β-d-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone (Fig. 2). It features a highly condensed aromatic ring system coupled to a glucose moiety via a C-C bond. As a C-glucoside, mangiferin is poorly absorbed by the gastrointestinal tract. Consequently the bioavailability of MGF is very low (1.2%) (19–21) and the dose required for MGF to exert significant effects is high in vivo experiments (Table 1). The concentrations of MGF in in vitro experiments correlate with in vivo dosage and tend to be high, as well (Table 1). The detailed information on MGF bioavailability and

pharmacokinetics of MGF is discussed in other articles of this special issue on MGF. It is also discussed in a recently published review on MGF (22).

MGF bears a catechol moiety, which enables it to form stable MGF-Fe^{2+}/Fe^{3+} complexes, preventing Fenton-type reactions and corresponding lipid peroxidation reactions (23). Such structural feature enables MGF to scavenge reactive oxygen species (ROS) (24), thus being an effective antioxidant. MGF also helps to maintain the balance among the enzymes, superoxide dismutase, catalase and the glutathione system (25), which have key roles in the cellular defense system against free radical damage. MGF has been shown to affect several biological processes including mitochondrial bioenergetics, glycolysis, lipogenesis, and etc. Fundamental to these biological processes, MGF elicits a spectrum of bioactivities including anti-oxidant and anti-inflammatory effects, and recently discovered anti-hyperlipidemia, anti-hyperglycemia and anti-cancer effects (Fig. 3). The biological and pharmacological effects of MGF are summarized in Table 1.

1. MGF Modulates Obesity

Obesity is one of the major risk factors of development of other metabolic disorders including NAFLD and diabetes. Plant extracts rich in MGF prevents obesity in several animal models including high sucrose fed rats (26), high fat diet (HFD) fed C57BL6/J mice (27, 28), spontaneously obese type 2 diabetes mellitus (Tsumura Suzuki obese diabetes, TSOD) mice (29, 30), and obese diabetic KK-Ay mice (31). In overweight and obese humans, mango extracts containing MGF has been shown to reduce body weight, without side effects (32). With pure MGF, Guo et al. showed that MGF reduced HFD induced body weight gain in hamster (33). Recently we showed that MGF prevented HFD induced body weight gain in C57BL6/J mice (34). Additionally, Han et al. showed that a derivative of MGF, which had higher lipophilicities, reduced body weight gain in obese db/db (C57BL/KsJ) mice (35).

The reduction of body weight gain mainly occurs in fat mass (26, 28, 29, 33, 31, 30, 34). In most of these studies MGF was found to have no significant effects on food or water intake (27, 28, 33–35), suggesting that the effects of MGF could be mediated by altered metabolism. Indeed, MGF and MGF rich extracts enhance whole body oxygen consumption and energy expenditure (27, 34). Two main energy sources are carbohydrates and fats. MGF stimulates carbohydrate utilization in skeletal muscle (34). At the cellular level, Shimada et al. showed that MGF containing extracts inhibited differentiation of 3T3-L1 adipocytes (36). At the molecular level, MGF upregulates the enzymes in carbohydrate oxidation in muscle (34) and the enzymes in the pathway of lipid utilization in hepatocytes (33, 37). MGF also suppresses the enzymes in lipogenesis in hepatocytes (33, 37, 38). The ability of stimulating carbohydrate and lipid utilization and simultaneously inhibiting lipid synthesis enables MGF to prevent body weight gain and obesity.

2. MGF Inhibits Hyperlipidemia and Prevents NAFLD

Metabolism of physiological fatty acids and lipids is regulated by two processes, lipogenesis and lipolysis. Lipogenesis is catalyzed by such enzymes as acetyl-CoA carboxylase (Acc),

fatty acid synthase (Fas), elongase, stearoyl-CoA desaturase (Scd), glycerol-3-phosphate acyltransferase (Gpat), and diglyceride acyltransferase (Dgat), which are regulated by sterol regulatory element-binding proteins (SREBPs) (39–42). Lipolysis starts with hydrolysis of TG to free fatty acids (FFAs) catalyzed by lipoprotein lipases (LPL). FFAs are then translocated from the circulation into cells by a family of fatty acid transport proteins (FATPs) (43), with one of the most prominent and best characterized members as fatty acid translocase (FAT)/CD36 (44). Intracellular FFAs are converted to fatty acyl CoA, which is subsequently transferred to mitochondria by carnitine palmitocyl transferase 1 (Cpt1). In mitochondria fatty acyl CoA is converted to acetyl-CoA by long chain acyl-CoA dehydrogenase (Lcad), medium chain acyl-CoA dehydrogenase (Mcad), and other enzymes. Most of these enzymes participating lipolysis are target genes of peroxisome proliferator-activated receptors (PPARs) (45).

Certain stress conditions, such as over-nutrition and sedimentary lifestyle, can adversely impact fatty acid and lipid metabolism, leading to accumulation of lipid in plasma, liver and adipose tissues. In several hyperlipidemic animal models, including HFD and/or fructose fed rodents (mice, rats and hamsters), MGF is able to reverse elevated plasma total cholesterol, TG and FFAs, improve balance between LDL and HDL, and reduce atherogenic index (46, 33, 37, 34, 38, 47, 48). In livers of HFD-fed rats, MGF reduced TG and FFAs (49, 50). Xing et al. showed that MGF ameliorated fatty liver in fructose-fed spontaneously hypertensive rats (51). In an unbiased proteomics study (38), using HFD induced obese mouse model, the Chi group showed that MGF reduced plasma TG and prevented lipid accumulation in liver of those mice. More importantly, MGF is able to improve lipid profiles in human (52). In a double-blind randomized control clinical trial, Na and coworkers showed that MGF supplementation improved serum lipid profiles by reducing TG and FFA levels and increasing HDL level and, thus, atherogenis index, in overweight patients with hyperlipidemia (52). MGF also increased LPL activity and L-carnitine, β-hydroxybutyrate and acetoacete levels, suggesting that MGF could promote FFA oxidation (52).

Mechanistically, we and others have provided evidence that MGF inhibits lipogenesis. MGF reduces Acc and Dgat2 in liver of HFD fed rats or hamsters (33, 37). MGF also increases the ratio of phosphorylated-Acc (p-Acc)/Acc by inducing p-AMPK (37). Phosphorylated Acc is the inactive form of Acc. AMPK phosphorylates Acc and inhibits Acc activity. The proteomics study reported by the Chi group revealed that MGF prevented lipid accumulation in liver via down-regulation of acetyl-CoA carboxylase (Acac) and Scd (38). Acac catalyzes the irreversible carboxylation of acetyl-CoA to produce malonyl-CoA, the rate-determining step in fatty acid synthesis. Scd1 catalyzes the conversion of stearoyl-CoA to oleoyl-CoA, which is a major substrate for TG synthesis. Ingenuity pathway analysis (IPA) of these proteomics data predicted that MGF suppressed SREBPs (38). This data corroborates a report by Guo et al. showing that MGF treatment in hamster resulted in reduced SREBP-1c transcripts in liver (33). Additionally, Mahali et al. demonstrated that MGF could inhibit advanced glycation end productions (AGE)-mediated SREBP-DNA binding activity (33, 53, 54).

While inhibiting lipogenesis, MGF is able to stimulate lipolysis and enhance lipid clearance. Guo et al. showed that MGF increased mRNA of LPL (33). MGF has also been shown to

induce CD36 at both transcriptional and translational levels. It induces mRNA of CD36 in liver of hamsters (33) and increases protein level of CD36 in HepG2 (human hepatoblastoma) cells (37). In addition, MGF is able to restore fructose-stimulated sarcolemmal CD36 overexpression and decreased intracellular CD36 distribution in skeletal muscle (48). CD-36 is known to be under genomic control of PPARγ (55), suggesting that MGF might regulate lipid metabolism via modulation of PPARγ, although recent studies differ in their conclusions about MGF and PPARγ interaction (56, 53, 57, 54). For example, a gene reporter assay showed that MGF didn't have any effect on ciglitazone-induced PPARγ activation (58). The plant extracts, which are rich in MGF, inhibit intracellular TG and fat accumulation and reduce PPARγ2 expression in 3T3-L1 pre-adipocytes (57). In contrast, MGF enhances PPARγ activity in L6-myotubes (56) and increases PPARγ DNA binding ability in various cell lines including HepG2 cells (53, 54). These paradoxical effects of MGF on PPARγ could be due to PPARγ peculiarities in non-adipose tissues and associated with tissue-specificity of MGF action. Besides these effects, MGF promotes fatty acyl CoA translocation from the cytosol to mitochondria, as it induces Cpt1 (33, 37), probably by upregulating PPAR-α (33).

Although more comprehensive studies of the mechanisms of action of MGF are needed to better understand how MGF modulates lipid metabolism, these preliminary reports suggest that MGF suppresses lipogenesis and stimulates lipolysis, thereby preventing lipid accumulation and NAFLD.

3. MGF Reduces Hyperglycemia and Prevents Diabetes

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

MGF has been reported to reduce plasma glucose and insulin levels, and increase insulin sensitivity and glucose tolerance in different genetic mouse models of type 2 diabetes (59, 60), diet induced IR mouse model (34), and streptozotocin (STZ) induced diabetic rats (46, 61, 62). It seems that MGF does so via several unique mechanisms. MGF is an inhibitor of glucosidase (63), which could enable MGF to prevent overloaded carbohydrates from being converted to glucose and absorbed in the intestine. For the existing glucose, MGF appears to stimulate its utilization. The upstream event in the pathway of carbohydrate utilization is insulin signaling. MGF enhances insulin sensitivity and mitigates genetic or environment induced IR (59, 60, 46, 61, 34, 38, 62, 64, 47, 52, 48). In HFD induced IR mouse model, the Chi group showed that MGF reverses HFD caused higher than normal plasma insulin and mitigates HFD induced glucose intolerance (34). MGF also attenuates IR and reduces insulin level in a rat model of fructose-induced metabolic syndrome and in KK-Ay and TSOD diabetic mice (59, 60, 47, 48). In STZ-induced diabetic rats MGF is able to improve

insulin sensitivity and correct plasma glucose level, even though without affecting insulin level (46, 61, 62). Also, MGF showed the same effect in STZ-diabetes model enforced with HFD and fructose supplementation (64). In overweight patients with hyperlipidemia, Na et al. reported that MGF supplementation decreased IR index although without improvement of increased plasma insulin and glucose levels (52).

Upon insulin signaling, glucose transporters are translocated from the cytosol to the cell membranes to uptake glucose into cells. While the effects of MGF on GLUT1 is uncertain (56, 35), MGF increases GLUT4 content in the plasma membrane fraction of muscle in mice (60) and in cultured rat myotubes (56) and 3T3 preadipocytes and adipocytes (35), thus increasing glucose uptake (56, 65). MGF caused increase in GLUT4 expression and consequent glucose uptake is probably mediated via activation of AMPK (60, 56). MGF also induces the enzymes in glycogen synthesis (glycogen, glycogen phosphorylase, glycogen synthase) (61) and the enzymes in glycolysis such as hexokinase (HK), pyruvate kinase (PK) and glucose oxidation such as PDH (61, 34). The Chi group provided evidence of molecular mechanisms by which MGF upregulates PDH. MGF acutely activates PDH (34), probably by directly interacting with PDH. It also activates PDH by suppressing PDK4 (34), a negative regulator of PDH.

In addition to stimulating glucose utilization, MGF has also been shown to reduce glucose 6-phosphate (G6P) and fructose bisphosphatase (FBP) and therefore inhibit gluconeogenesis (61). Together, with enhancing insulin sensitivity and glucose utilization, MGF could be an effective anti-hyperglycemia and anti-diabetes agent.

4. MGF Protects Pancreatic β-cells and Mitigates Diabetic Complications

Hyperglycemia and hyperlipidemia are known to reduce viability and insulin secretion of pancreatic β-cells (66). ROS generation, endoplasmic reticulum stress and the following mitochondrial dysfunction have been considered to be important factors mediating pancreatic islets damage and deterioration of type 2 diabetes (67, 68, 66). MGF has well established antioxidant properties (24, 23) and shows its protective action against oxidative damage of various organs in STZ -induced diabetic rats including pancreas, heart, liver and kidney (69–71). Oral administration of MGF improves pancreatic ultramicroscopic architecture and increases β-cell count in STZ diabetic rats (71). These beneficial effects of MGF on pancreas are due to its ability to reduce hydroperoxides and increase reduced glutathione (GSH) (71). In addition, MGF increases nonenzymatic antioxidants in plasma such as vitamin C (71). MGF can also facilitate islet regeneration and β-cell proliferation by regulating cell cycle and essential proteins related to islet regeneration and glucose metabolism (72, 73).

One of the most serious complications of diabetes is diabetic nephropathy (DN) and it is the most common cause of the end stage renal disease. Hyperglycemia-induced overproduction of ROS is the central mechanism of diabetic complications and increased poly pathway flux and formation of AGEs are the two important participators in ROS generation (74). Since MGF is an effective antioxidant, its effects on DN have been studied by several groups using STZ induced diabetic rats (75–77). MGF significantly reverses STZ caused kidney

enlargement and structural damage, and kidney dysfunction measured as urinary protein secretion and blood urea nitrogen (75, 76, 62). These effects of MGF are mediated by several mechanisms. Liu et al. showed that MGF reduced AGEs and receptor for advanced glycation end products (RAGE) by upregulating glyoxalase 1 (76). Pal et al. demonstrated that MGF reversed STZ caused reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) and thereby increased the ratio of GSH to GSSG (oxidized glutathione), and reduced malondialdehyde, protein carbonylation and ROS (78, 62). This group also showed that MGF inhibited STZ induced activation of NF-κB pathway (62), which could induce inflammation in kidney. In addition, MGF attenuates sepsis-induced acute kidney injury (79) and renal fibrosis (62, 80) via antioxidant and anti-inflammatory effects. Moreover, MGF inhibits renal urate reabsorption by modulating urate transporters (81).

5. MGF Mitigates Cardiac Vascular Diseases

CVD continues to be the leading cause of death worldwide (5). 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 (82), probably due to its ability to enhance mitochondrial oxidative capacity and at the same time to reduce ROS. Being not only an antioxidant but also an anti-inflammatory agent, MGF significantly ameliorates diabetic cardiomyopathy in STZ- and HFD-diabetic rats. Chronic treatment with MGF decreased the levels of myocardial enzymes (CK-MB and LDH) and inflammatory mediators (TNFα and IL-1β) through deactivation of NF-κB nuclear translocation and suppression of RAGE expression (83).

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 anti-hyperlipidemia 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 (84, 85). For instance, cardiac overexpression of PPAR-α, which stimulates β-oxidation, induces pathological cardiac changes (86). Interestingly, in the hearts of Zucker diabetic fatty rats (ZDF, a genetic model of type 2 diabetes and obesity), *Salacia oblonga* extracts containing MGF reduced upregulated PPAR-α and Cpt-1 and Aco mRNAs, while it enhanced hepatic expression of PPAR-α, Cpt-1 and acyl-CoA oxidase (Aco) (87, 85). These putative tissue specific, perhaps paradoxical effects of MGF require further verification. Nevertheless, MGF seems to have beneficial effects in improving CVD.

6. MGF Modulates Cross Talk between Lipid Metabolism and Carbohydrate Metabolism

Cross talk between lipid and carbohydrate metabolisms exists and has been reported (88–91). Hyperglycemia is still considered the principal contributor to the formation of sugar-derived substances AGEs, which accumulate in diabetic persons and contribute to its micro- and macrovascular complications (92, 93). Recent studies revealed that accumulation of

AGEs activates lipogenesis in liver and skeletal muscles by interfering with SREBP-1c through downregulation of the SREBP-inhibiting enzyme SIRT-1 and increased glycation of the SREBP-activating protein SCAP (94–96). Mahalli et al. also reported AGE-induced intracellular lipid accumulation in different cell lines, including HepG2, through RAGE-mediated ROS-dependent and -independent ERK and IKK activation, resulting in increased SREBP-DNA binding (53, 54). MGF is able to downregulate these processes and completely suppress AGE-induced lipogenesis, whereas antioxidants, IKK and ERK inhibitors showed only partial protection (53, 54). MGF also stimulates carbohydrate utilization (34), and presumably reduces the sources of AGEs. Enhanced carbohydrate oxidative utilization could potentially raise acetyl-CoA, the end product of carbohydrate oxidation. Acetyl CoA is a substrate of lipogenesis. One would assume that MGF could potentially increase lipogenesis. However, as discussed above, MGF suppresses lipid production. The hypothesized mechanism is that MGF inhibits lipogenesis by suppressing important players in the lipogenesis pathway as supported by the currently available data (33, 37), especially the comprehensive proteomics study reported by the Chi group (38).

While carbohydrate metabolism influences lipid homeostasis, on the other hand, lipid metabolism affects carbohydrate balance. For instance, accumulation of circulating FFAs and lipids could raise glucose level by inducing IR and impairing mitochondrial function, and thereby inhibiting glucose utilization (97, 98). One of the important mediators of cross talk between lipid accumulation and IR is inflammation (Fig. 3). Recent studies established the signaling pathways activated by obesity and involved in development of inflammation and IR in numerous cell types (99–103). One of the theories holds that adipose expansion leads to formation of hypertrophic adipocytes that secreting chemoattractants and leukotriene B4 (LTB4), which in turn causes influx of immune cells to adipose tissue, initiating a cascade of inflammatory events (101). Overload of fat increases lipolysis and augmented lipolysis causes increased plasma levels of saturated FFAs, which can directly activate pro-inflammatory responses in vascular endothelial cells and myeloid-derived cells (102). Excess of intracellular fatty acids activates fatty acid oxidation and leads to excessive generation of peroxidation products in mitochondria (104). Pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, along with peroxidation products, stimulate IKK-β / NFκB and MAPK/ERK/JNK signaling pathways, which contribute to IR due to the ability of IKK-β and JNK serine kinases to phosphorylate serine 307 of IRS1, instead of tyrosine, and hence blunt normal insulin signaling. NF-κB could in turn transcribe its target genes, including those pro-inflammatory cytokines (92).

Using a DNA hybridization array, Leiro et al. found that MGF had significant impacts on the profiles of a large number of NF-κB related cytokine genes that are critical for regulation of inflammation (105). More recent studies reported MGF's ability to suppress IKK-β / NF-κB and/or MAPK/ ERK/JNK signaling pathways in lymphoid organs (106), leucocytes (107), diabetic kidneys (62) and heart (83), acutely injured liver (78), colon (108) and lungs (109), and to inhibit NF-kB DNA binding and IKK activity in HepG2 cells (110).

MGF's ability to suppress NF-κB presumably inhibits the production of pro-inflammatory cytokines, and therefore mitigates inflammation caused IR. Indeed, Leiro et al. showed that in primary macrophages from mice, MGF treatment significantly blunted the expression of

pro-inflammatory cytokines including IL-1β, IL-6, IL-12, TNFα and other cytokines (105). Tsubaki et al. showed that MGF suppressed the expression of TNFα, IL-6, and IL-1β through inhibiting the activation of NF-κB and ERK1/2 in thymus and spleen of collagen induced arthritis mice (106). MGF treatment reduces serum levels of TNF-alpha, IL-1β and IL-6, and expressions of ERK and JNK in leukocytes after lipopolysaccharide (LPS) stimulation (107). In LPS-stimulated primary hepatocytes, Pan et al. showed that MGF significantly reduced expression of IL-1β and TNFα. In addition, MGF ameliorated LPS/D-galactoseamine-induced acute liver injure in vivo, correcting serum and hepatic inflammatory profiles via blocking hepatic NLRP3 inflammasome activation and activating the Nrf2 pathway (111). In STZ- and HFD-diabetic cardiomyopathy rats, Hou et al. showed that MGF reduced plasma TG (83). In the heart of those rats, MGF reduced not only pro-inflammatory cytokines, but also AGEs (83). Furthermore, MGF improved insulin sensitivity in peripheral tissues (Adipo-IR) by normalizing the fructose-induced increase of NEFA plasma clearance and suppressing fatty acid uptake by muscular tissue (48). Using high-fat/high fructose diet followed by a subdiabetogenic dose of STZ (HFD-Fr-STZ) rat model, Saleh et al. showed that MGF reduced lipids, TNFα, and mitigated IR and hyperglycemia (64). In overweight patients with hyperlipidemia and presenting IR, MGF supplementation decreased IR index (52).

Thus far we have discussed MGF modulation of upstream events in the cross talk between carbohydrate and lipid metabolism. MGF also modulates the downstream events of carbohydrate and lipid metabolisms. The metabolisms of carbohydrates and lipids converge at acetyl-CoA, which is further metabolized by the tricarboxylic acid (TCA) cycle and the subsequent electron transport chain (ETC) to produce energy ATP in mitochondria. Mitochondrial dysfunction is closely associated with over 50 diseases including metabolic syndromes (112–114). Our recent unbiased proteomics study revealed that MGF upregulated proteins participating in mitochondrial bioenergetics (38). These proteins include oxoglutarate dehydrogenase E1 (Dhtkd1), cytochrome c oxidase subunit 6B1 (Cox6b1), fumarate hydratase 1 (Fh1), short-chain specific acyl-CoA dehydrogenase (Acads), enoyl-CoA hydratase and carnitine *O*-palmitoyltransferase 2 (Cpt2). Others found that MGF raised the levels of state 3, state 4 and ATP in mitochondrial respiration (82). In addition, MGF modulates NAD^+/NADH, which are important factors in the TCA cycle and the ETC. MGF and MGF rich extracts reduce NADH (26) and increase NAD^+ and therefore increase the ratio of NAD^+/NADH (34). These studies indicate that MGF is able to increase mitochondrial bioenergetics in general and thereby stimulate metabolisms of both carbohydrates and fatty acids, setting off the competition between carbohydrate and fatty acid utilization and mitigating both hyperglycemia and hyperlipidemia simultaneously.

The mitochondrial respiratory chain is a major source of ROS within the cell (115–117). Excessive production of ROS and increased oxidative stress are participants in the development and progression of NAFLD, diabetes and its complications, CDV and cancer (118–123). MGF has well established antioxidant properties, for the reasons discussed above, even though it enhances mitochondrial respiration. MGF's antioxidative properties also account for its anti-inflammatory effects. 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 syndromes.

Conclusions

In summary, the use of synergies of anti-obesity and anti-diabetes drugs with different mechanisms of action is an effective approach for developing new combined pharmaceutical compositions (11). The literature thus far shows that MGF could be an example of one compound exerting multiple beneficial effects. MGF interferes with multiple biological processes critical to the development of metabolic syndrome (Fig. 3). The central effects are probably antioxidant and anti-inflammation, which enable MGF to counteract with IR caused by ROS and inflammation resulted from excessive accumulation of lipids. These are fundamental processes involved in all metabolic disorders. The most studied and the most consistent effects of MGF are reduction of IR and TG and FFAs (Table 1). MGF mitigates IR and consequently promotes glucose uptake. Together with its ability to enhance glycolysis, and perhaps to inhibit gluconeogenesis, MGF can effectively prevent hyperglycemia. MGF stimulates lipolysis and suppresses lipogenesis and thereby reduces lipid accumulation and consequently prevents hyperlipidemia.

What are lacking are in depth mechanistic studies that could pinpoint the molecular targets of MGF. We recently provided evidence that MGF activates PDH (34). Our proteomics study also predicts other molecular targets and signaling pathways affected by MGF (38). While these studies advanced our understanding of the mechanisms of action of MGF, more mechanistic studies are in great need to provide clear pictures of how MGF exerts its beneficial effects. Affecting multiple targets can result in complex effects, some of which could be contradictory to others. This could be the downfall of the strategy of targeting multiple biological markers and events. Nevertheless this strategy has its advantages and is especially applicable to metabolic syndrome as metabolic syndrome includes multiple pathological conditions.

Up-to-date the reported studies of the effects of MGF were mainly conducted in cultured cells and in rodents. There has been only one report on the clinical study of MGF in human (52). More clinical studies in large cohort are necessary to demonstrate that MGF has great potential to be developed into nutritional/pharmacological therapeutics that could prevent and/or reverse metabolic disorders by modulating multiple biological events and processes.

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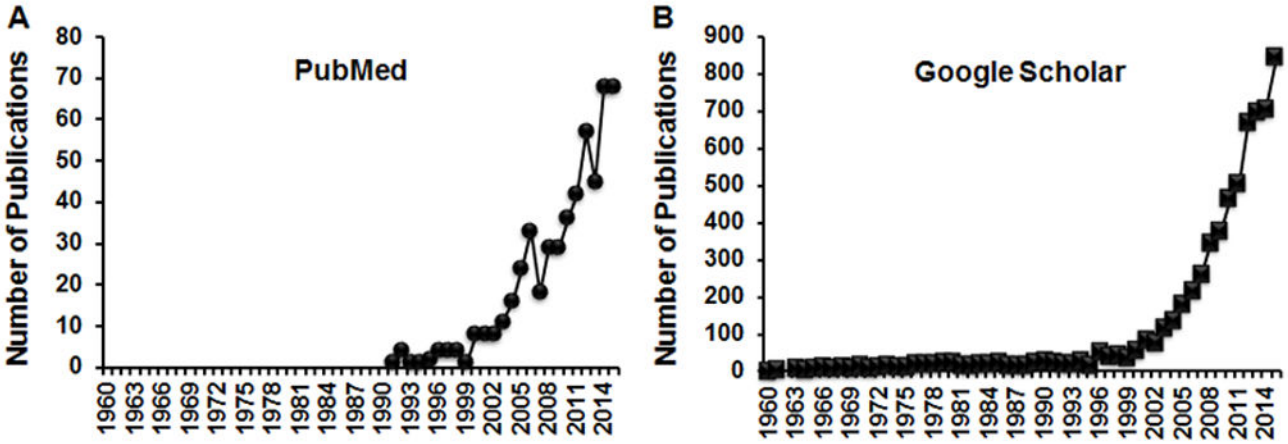

Fig. 1.

Survey of the studies of MGF in PubMed (A) and Google Scholar (B). The number of publications was obtained by typing “mangiferin” and each year, for instance “1960”, in either PubMed or Google Scholar.

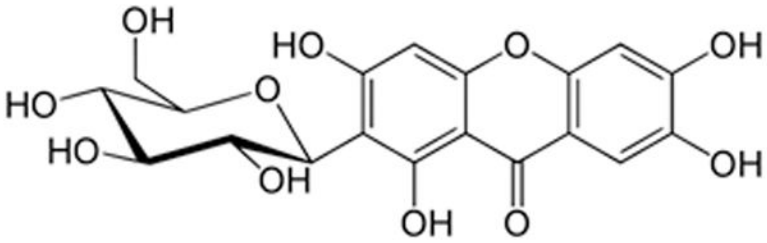

Fig. 2.
Structure of mangiferin.

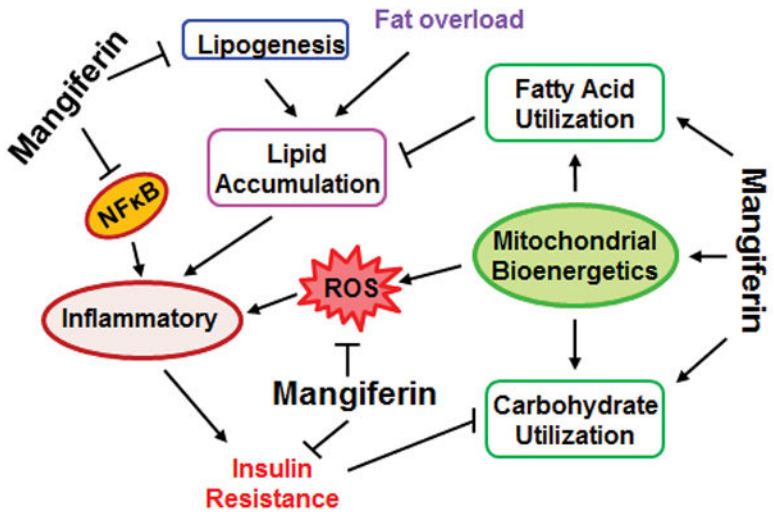

Fig. 3.

Mangiferin modulated biological processes involved in metabolism and metabolic disorders.

Table 1

Bio- and Pharmacological Effects of Mangiferin Related to Metabolic Disorders.

	In vivo								In vitro		
Experimental model	**HFD**			**HFD-, fructose- and STZ-induced metabolic syndrome**	**Fructose-induced metabolic syndrome**	**Overweight patients with hyper-lipidemia**	**STZ-induced diabetes**	**Genetic model of diabetes**	**AGE-induced lipogenesis**	**FFA (OA)**	
Experimental subject	**Mice *(1, 2)***	**Rat *(3)***	**Hamster *(4)***	**Rat *(5)***	**Rat *(6, 7)***	**Human *(8)***	**Rat *(9–11)***	**KK-Ay TSOD mice *(12, 13)***	**HepG2 cells *(14, 15)***	**HepG2 cells *(3)***	**C2C12, L6 myotubes *(16, 2)***
Doses	**400 mg/kg o.**	**50–150 mg/kg o.**	**50–150 mg/kg o.**	**20mg/kg i.p.**	**15 mg/kg o.**	**150 mg/day**	**10–20 mg/kg i.p. 40 mg/kg o.**	**90 mg/kg o.**	**10 μM**	**12.5–100 μM**	**2, 200 μM**
BW	↓	↔	↓	↔	↔	↔	↔				
Plasma glucose	↓		↔	↓	↔	↔	↓	↓			
Plasma insulin	↓			↔	↓	↔		↓			
IR	↓			↓	↓	↓	↓	↓			
Plasma TG	↓	↓	↓	↓	↔	↓	↓	↓			
Plasma FFA		↓	↓		↓	↓	↓				
Plasma cholesterol	↓		↔	↓		↔	↓	↓			
Plasma LDL	↓		↔	↓		↔	↓				
Plasma HDL			↔	↑		↑	↑				
AdipoIR					↓						
β-cell function				↑							
β-hydroxybutyrate		↑				↑					
Liver TG	↓	↓	↓	↓	↓						
Liver FFA		↓	↓								
Liver glycogen				↑							
Muscle TG					↓						
Muscle FFA			↓								
CD36 expression		↑	↑ liver muscle		↓muscular membrane					↑	
PKB/Akt											↔

	In vivo								In vitro		
Experimental model	**HFD**			**HFD-, fructose- and STZ-induced metabolic syndrome**	**Fructose-induced metabolic syndrome**	**Overweight patients with hyper-lipidemia**	**STZ-induced diabetes**	**Genetic model of diabetes**	**AGE-induced lipogenesis**	**FFA (OA)**	
Experimental subject	**Mice *(1, 2)***	**Rat *(3)***	**Hamster *(4)***	**Rat *(5)***	**Rat *(6, 7)***	**Human *(8)***	**Rat *(9–11)***	**KK-Ay TSOD mice *(12, 13)***	**HepG2 cells *(14, 15)***	**HepG2 cells *(3)***	**C2C12, L6 myotubes *(16, 2)***
Doses	**400 mg/kg o.**	**50–150 mg/kg o.**	**50–150 mg/kg o.**	**20mg/kg i.p.**	**15 mg/kg o.**	**150 mg/day**	**10–20 mg/kg i.p. 40 mg/kg o.**	**90 mg/kg o.**	**10 μM**	**12.5–100 μM**	**2, 200 μM**
Glut4								↑			↑
Glycolysis enzymes (HK, PK, PDH)							↑				↑
Gluconeogenesis							↓				
Cpt-1		↑	↑ liver		↔					↑	
p-AMPK		↑								↑	↑
SREBP 1c			↓ liver		↔				↓		
Acc	↓liver	↓	↓ liver		↔					↓(↑ phos)	
Scd1	↓liver				↔						
Dgat2		↓	↓liver		↓					↓	
PPARα			↑ liver ↑ muscle		↔						
PPARγ					↔ muscle				↑		↓
MAPK/ERK									↓		
IKK									↓		
Adiponectin	↑			↑ serum	↔ muscle						
TNFα				↓serum	↔ muscle						

↑ MGF treatment increased indicated parameter; ↓ MGF treatment decreased indicated parameter; ↔ MGF didn't show effect on indicated parameter.

o., oral administration; i.p., intraperitoneal administration.

Grey-shaded cells - parameter is not applicable; yellow-shaded cells - parameter shows the same trend in most of experiments.

HFD, high fat diet; STZ, streptozotocin; AGE, advanced glycation end products; FFA, free fatty acid; OA, oleic acid; BW, body weight; IR, insulin resistance; TG, triglycerides; LDL, low-density lipoproteins; HDL, high-density lipoproteins; PKB/Akt, protein kinase B/Akt; HK, hexokinase; Glut4, glucose transported type 4; PK, pyruvate kinase; PDH, pyruvate dehydrogenase; Cpt-1, carnitine palmitocyl transferase 1; p-AMPK, phosphorylated AMP-activated protein kinase ; SREBP 1c, sterol regulatory element-binding proteins 1c; Acc, acetyl-CoA carboxylase; Scd1, stearoyl-CoA desaturase 1; Dgat2, diglyceride acyltransferase 2; PPAR, peroxisome proliferator-activated receptors; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; IKK, IκB kinase; TNFα, tumor necrosis factor α.

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