A Systematic Review of the Medicinal Potential of Mulberry in Treating Diabetes Mellitus

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A systematic review of the medicinal potential of mulberry in treating diabetes mellitus

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Running Title: MEDICINAL POTENTIAL OF MULBERRY

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Abstract: Diabetes mellitus (DM) is a serious metabolic disorder which has reached epidemic proportions all over the world. Despite tremendous developments in medicinal chemistry, traditional medicine is still commonly used for the prevention and treatment of DM. Traditional herbal medicines have been playing a major role in the management of DM in Asian countries. In particular, mulberry has commonly been utilized in China for the treatment of DM for thousands of years. In the last decade, numerous preclinical findings have suggested that mulberry is a promising therapeutic agent for the treatment of DM, and the polyhydroxylated alkaloids, flavonoids and polysaccharides from mulberry may be the potential active components. The present review systematically summarizes the chemical composition of mulberry and the pharmacological effects of different medicinal parts on DM; these effects include influences on glucose absorption, insulin (INS) production/secretion, anti-oxidation and anti-inflammation processes. After summarizing research findings, we discuss challenges and opportunities, and explore the direction of future research and the potential for developing mulberry into pharmaceuticals for the widespread treatment of DM.

Key Words: Mulberry; Morus; Diabetes Mellitus; Medicinal Potential; Polyhydroxylated Alkaloids.
Introduction

Diabetes mellitus (DM), commonly referred to as simply “diabetes”, is a group of metabolic disorders resulting from defects in insulin (INS) secretion and/or reduction of sensitivity of the tissues to INS action (Lanza et al, 1999). DM is commonly referred to diabetes, which causes high blood sugar levels over a prolonged period and predispose to many complications, such as severe microvascular complications (Perera et al, 2011). DM is divided into two major categories: Type 1 diabetes and Type 2 diabetes. Type 2 diabetes account for 90% of people with diabetes around the world. The frequent development of Type 2 diabetes and cardiovascular diseases (CVDs) among the obese is possibly related to excess adipose tissue and low-grade chronic inflammation (Kim et al, 2012). Overall, the occurrence of DM is increasing. The total number of people suffering from DM reached 422 million in 2014, compared to 108 million in 1980 (Hamdan et al, 2004). It is estimated that this number will reach 439 million adult patients by 2030, by which time WHO projects it will become the 7th leading cause of death. Under the direction of recommendations of WHO on DM, investigation of hypoglycemic agents from medicinal plants has become more essential (World Health Organization, 1980).

The genus Morus is the type genus of the family Moraceae; the family comprises about 40 genera and over 1000 species. The main eleven species of Morus include M. alba, M. australis, M. bomycis, M. laevigata, M. nigra, M. serrata, M. rubra, M. macroura, M. cathayana, M. multicaulis, and M. insignis (Venkatesh and Chauhan, 2008). Of these M. alba is the most common in the world. Its medical parts are: leaf, twig, root bark, and fruit (Pharmacopoeia Committee of People’s Republic China, 2015).

Mulberry (Figure 1) has been used as an herbal medicine in China for thousands of years. Each part of the plant has different uses, and the earliest report on the properties and uses of M. alba leaf appeared in the Han dynasty (25th to 27th century BC) in the Shennong Bencaojing (Sun, 2006). Recent scientific evidence has confirmed that the dried powder, water extract, and ethanol extract of M. alba leaf possess diverse biological activities, including anti-diabetic, neuroprotective, anti-microbial, anti-oxidative, anti-inflammatory, anti-atherosclerotic, and anti-cancer (Butt et al, 2008; Singh et al, 2013). Of particular relevance here, mulberry leaves have been used to cure and prevent “Xiao-ke” (a syndrome that we can now identify as diabetes) in Chinese medicine. The root bark of mulberry trees are used for anti-inflammatory, diuretic, antitussive, and anti-pyretic purposes in
oriental medicine, whereas mulberry fruits are used as a tonic and sedative medicine (Asano et al., 2001).

Chemical Constituents
Mulberry leaf contains steroids and triterpene compounds, flavonoids, coumarin, essential oils, amino acids, alkaloids, and organic acids. Mulberry twig contains tannin, fructose, stachyose, glucose, maltose, melitose, and arabinose. Mulberry root bark contains flavonoids, like mulberrin, mulberrochromene, and cyclomulberrin. Mulberry fruit contains vitamin B1, B2 and carotene, as well as fatty acids, such as linoleic, oleic acid, and stearic acid. The main active components in these different parts of mulberry vary, but polyhydroxylated alkaloids, flavonoids and polysaccharides are present in all parts and these are listed below.

Polyhydroxylated Alkaloids
1-deoxynojirimycin (DNJ) (1), N-methyl-1-deoxynojirimycin (2), fagomine (3), 3-epi-fagomine (4), 1,4-dideoxy-1,4-imino-D-arabinitol (5), 1,4-dideoxy-1,4-imino-D-ribitol (6), 1α,2β,3α,4β-tetrahydroxy-nor-tropane (calystegin B2) (7), 1α,2β,3α,4β,6α-pentahydroxy-nor-tropane (calystegin C1) (8), 1,4-dideoxy-1,4-imino-(2-O-β-D-glucopyranosyl)-D-arabinitol (9), 2-O-α-D-galactopyranosyl-1-deoxynojirimycins (10), 6-O-α-D-galactopyranosyl-1-deoxynojirimycins (11), 2-O-α-D-glucopyranosyl-1-deoxynojirimycins (12), 3-O-α-D-glucopyranosyl-1-deoxynojirimycins (13), 4-O-α-D-glucopyranosyl-1-deoxynojirimycins (14), 2-O-β-D-glucopyranosyl-1-deoxynojirimycins (15), 3-O-β-D-glucopyranosyl-1-deoxynojirimycins (16), 4-O-β-D-glucopyranosyl-1-deoxynojirimycins (17), 6-O-β-D-glucopyranosyl-1-deoxynojirimycins (18) (Kimura et al., 1995) (Figure 2).

Flavonoids
Quercetin (19), kaempferol (20), isoquercitrin (21), kaempferol-3-0-β-D-glucopyranoside (astragalin) (22) (Tao et al., 2013), quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (rutin) (23), quercetin 3-(6-malonylglucoside) (Q3MG) (24) (Katsube et al., 2010), quercetin3-(6-acetylglucoside) (Q3AG) (25), kaempferol3-(6-rhamnosylglucoside) (K3RG) (26), kaempferol3-(6-malonylglucoside) (K3MG) (27) (Sugiyama et al., 2013), morusin (28) (Ma et al., 2013), sanggenon
C (29), sanggenon G (30), kuwanon L (31) (Cui et al, 2006) (Figure 3).

**Polysaccharides**
Sprague-Dawley (SD)2-3, SD3-3 and SD3-4 (Lv et al, 2007).

**Others**
Moracin M (32), mulberrofuran C (33), chlorogenic acid (34) (Cui et al, 2006), cytidine (35), 2 - (l', 2', 3', 4'-tetrahydroxy-butyl) -5- (2", 3", 4" - trihydroxy-butyl) pyrazine (36) (Figure 4).

**Pharmacology**

**Anti-diabetic Effects and Mechanisms of Different Parts of Mulberry**
Many studies have examined the efficacy of mulberry hypoglycemic activity *in vitro* and *in vivo* on cell and animal models, as well as in clinical trials. Investigations of the therapeutic strategies and mechanisms, in addition to complications, in treating DM have also been undertaken. This review summarizes the results of those studies and investigations, describing the medicinal potentials of different parts of the mulberry and of its isolated main components, namely polyhydroxylated alkaloids, flavonoids and polysaccharides, in the treatment of DM.

It was recorded that mulberry was used to treat “Xiao-ke”, the Chinese traditional medical term for a condition which can be considered as DM. However, each botanical part of mulberry has its own special effects on DM. It is estimated that the proportion of potential active components may determine the anti-diabetic activity of different extracts from the leaves, root, branches and fruits. The activities of different parts of various species of mulberry are described in the following sections (Table 1).

**Mulberry Leaf**
A study investigated the antihyperglycemic and antioxidant effects of mulberry (*M. indica*) leaves on streptozotocin (STZ)-induced diabetic male Wistar rats. In this study, abnormally high-level lipid peroxidation and catalase (CAT) activity in erythrocytes observed in diabetic mice were significantly decreased by mulberry leaves (48% and 33%, respectively) (Andallu et al, 2012). Meanwhile, another study showed the hypoglycemic effect of mulberry leaf powder (MLP), which was evaluated by comparing its anti-diabetic activity to that of the standard drug, glibenclamide. The results showed
that the mulberry therapy significantly decreased the concentration of serum total cholesterol (TCH), triglycerides (TG), plasma free fatty acids, low density lipoprotein (LDL)-cholesterol, very low density lipoprotein (VLDL)-cholesterol, plasma peroxides, and urinary peroxides, while it increased high-density lipoprotein (HDL)-cholesterol (Andallu et al, 2012). KK-Ay mice were raised on 0%, 3%, or 6% extract from M. alba leaf powder with high-sucrose diets for 8 weeks. It was observed that the repeated ingestion reduced INS resistance and might delay the onset of clinical features of DM, especially Type 2 DM (Tanabe et al, 2011). Another study investigated the amelioration of oxidative stress by mulberry (M. indica) leaves and assessed the influence of mulberry leaves on antioxidant enzymes in STZ-diabetic rats. Results showed that the treatment with mulberry leaves protected STZ-diabetic rats from lipid peroxidation and could elevate the activities of antioxidant enzymes (Bondada et al, 2014). It has been examined whether a dietary intake of mulberry leaf power could affect atherogenesis in vivo and in vitro (Harauma et al, 2007). After 12 weeks, a significant increase in the lag time of lipoprotein oxidation was detected in the MLP group compared to the control group. Furthermore, the MLP group showed a 40% reduction in atherosclerotic lesion size in the aortae compared to the control group. They also examined the anti-oxidative activity of MLP in vitro. Aqueous extract of MLP had a strong scavenging effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH) and strongly inhibited lipoprotein oxidation. A report examined the postprandial hypoglycemic effect of mulberry leaf (M. alba), which suggested that it may be beneficial as a food supplement to manage postprandial blood glucose. The postprandial hypoglycemic function of mulberry leaf water extract (MLW) may be due to the inhibitory effect of glucose transport and α-glucosidase in the small intestine (Park et al, 2009).

The water extracts and ethanol-insoluble extracts from M. alba exhibited strong hypoglycemic effects, apparently by increasing glucose uptake (Chen et al, 1995). Others also observed that mulberry tea reduced the liberated glucose contents in both apical and basal sides of the cell monolayers in a Caco-2 cell culture experiment. It can be concluded that hot water extract of mulberry leaves does inhibit α-glucosidases, maltase, and sucrose enzymes, and it has the potential to be consumed as an antidiabetic herb tea (Hansawasdi et al, 2006). In addition, it has been showed that hot water extracts of mulberry leaves can increase saliva secretion (Chen et al, 1995). The potentiation of pilocarpine-induced salivary flow was correlated with anti-hyperglycemic effects. Others also observed that daily administration of 1 g/kg ethanolic extract of mulberry leaf for six weeks decreased
blood glucose by 22%, which was comparable to the effect of 4 U/kg INS in STZ-induced diabetic rats. Hemoglobin A1c (HbA1c), a biomarker for chronic exposure to high concentration of glucose, was also significantly decreased in the mulberry leaf-treated group (6.78 ± 0.30%) in comparison to untreated group (9.02 ± 0.30%) (Naowaboot et al, 2009). Another study reported that, in Wistar rats treated with 90% ethanol extract of mulberry leaf 400 mg and 600 mg/kg body weight for 35 days, blood glucose, HbA1c, TG, LDL, VLDL, blood urea, and cholesterol were decreased, while the number of β-cells, and diameter of the islets were increased in the experimental group compared to the control group (Hosseinzadeh et al, 1999). 50% ethanol extract of M. alba (EMA) leaf had the function of restoring the vascular reactivity of diabetic rats. EMA significantly reduced blood glucose levels, also lowered high blood pressure in diabetic rats (Naowaboot et al, 2009). Water extract from M. alba shows protective effect in that it can prevent blood vessels from being damaged by a high fat and high cholesterol diet, as demonstrated in one rat model experiment. In terms of the effect of mulberry on the pancreas of diabetic rats, after animals were treated with mulberry leaf extract (MLE) at dosages of 400 and 600 mg/kg body weight for 35 days, histological and biochemical results indicated that the MLE may reduce blood glucose levels by regeneration of β-cells (Mohammadi et al, 2012).

The hypoglycemic effects of M. nigra and M. alba leaves extracts were studied in normal and alloxan-diabetic mice. A single dose (500 mg/kg) of dried leaf extract of both species decreased blood glucose levels in alloxan-diabetic mice (Hosseinzadeh et al, 1999). For STZ-induced diabetic rats, the anti-diabetic activity of M. nigra leaf extract was evaluated after oral administration. The administration of 500 mg/kg/day of leaf extract reduced the concentration of blood glucose from 370 ± 7.31 mg/dl (control) to 154 ± 6.27 mg/dl, and a significant increase in the INS level from 11.3 ± 0.31 μU/ml (control) to 14.6 ± 0.43 μU/ml was recorded (El-Mawla et al, 2011). Moreover, another study demonstrated the antioxidant nature of M. rubra aqueous leaf extract, and confirmed it may reduce diabetic complications. M. rubra aqueous leaf extract may help treat hyperglycaemia and dyslipidaemia (Bala et al, 2010). In STZ-diabetic rats, M. alba leaf extract decreased weekly food consumption throughout the 5-week treatment period. The hypoglycemic effect was probably achieved through interference with food intake or prevention of gastrointestinal glucose absorption (Ojewole et al, 2006).

MLW of M. alba showed hypoglycemic activity which was associated with improved INS
secretion and INS sensitivity in diabetic animals (Huang et al, 2014). In one study, an array of active components in MLW appeared to provide higher potency in inhibiting intestinal glucose absorption compared to the single component DNJ (1), which was recognized as a promising inhibitor of intestinal glucose absorption because only MLE showed significant inhibition of 2-deoxyglucose uptake, whereas DNJ (1) was ineffective in Caco-2 cells. For glucose loading, co-administration of MLW with glucose resulted in potent inhibitory effects of glucose responses compared to those by DNJ (1) in SD rats, but this was not found for maltose loading. These novel findings add evidence that the unabsorbed phytochemicals in MLE compete with glucose for intestinal glucose transporters, but DNJ (1) itself does not (Kwon et al, 2011). However, another research study found that DNJ-rich MLE suppressed elevation of postprandial blood glucose in humans. The findings showed a modest decrease in serum TG levels and beneficial changes in the lipoprotein profile following 12-week administration of DNJ-rich MLE, with no associated adverse events (Kojima et al, 2010). Another study aimed to evaluate the therapeutic effect and potential mechanism(s) of the hybrid of DNJ and polysaccharide (HDP) from mulberry leaves on alloxan-induced diabetic mice. A significant decline in blood glucose, HbA1c, TG, aspartate transaminase (AST) and alanine transaminase (ALT) levels, and an evident increase in body weight, plasma INS level and HDL were observed in HDP-treated diabetic mice. The polysaccharides could protect alloxan-induced pancreatic islets from damage by scavenging the free radicals and repairing destroyed pancreatic β-cells. Pharmacokinetics assay showed that DNJ could be absorbed from the gastrointestinal mucosa and diffused rapidly into the liver, resulting in postprandial blood glucose decrease (Li et al, 2011). Furthermore, mulberry leaves attenuated atherosclerotic lesion development in Ldlr−/− mice through enhancement of LDL resistance to oxidative modification, and these antioxidative and antiatherogenic protective effects were attributed mainly to Q3MG (24), the most abundant flavonol glycoside in mulberry leaves (Enkhmaa et al, 2005).

A human study indicated that oral administration of a single dose of 0.8 or 1.2 g of DNJ-enriched mulberry leaves powder significantly suppressed the elevation of postprandial blood glucose and secretion of INS, which indicates that they have insulinotropic properties. At the same time, their antioxidant potential can reduce occurrence of complications of DM (Kimura et al, 2007).

*Mulberry Twigs and Branches*
Branch bark extract (BBE) of *M. multicaulis* aqueous alcohol solution was orally administered to STZ-induced diabetic mice for three weeks. At the end of the study, the mice had gained weight and swelling of liver and kidney were ameliorated. BBE not only reduced the abnormally elevated levels of serum INS and ameliorated INS resistance induced by STZ, but also appeared to regulate dyslipidemia in diabetic mice. Moreover, the experiment indicated that BBE can regulate the expression of glycometabolism genes in diabetic mice. Increased RNA expression of the genes Ins1, Ins2 and pancreatic duodenal homeobox-1 (PDX-1) might decrease INS resistance in diabetic mice (Liu et al., 2014). Besides, ethanolic extract of mulberry twigs (EEMT) might serve as a natural antioxidant and tyrosinase inhibitor (Chang et al., 2011). In another study, the influence of Ramulus Mori polysaccharides (RMP) has been examined. The results showed that body weight and INS level were notably increased after RMP treatments, while blood glucose decreased. Such effect might be because the expression levels of tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) were effectively reduced in pancreas tissue after the treatments (Guo et al., 2013).

**Mulberry Root Bark**

It has been showed that ethanol-insoluble extract fractions of Mori Cortex Radicis (MCR) could lower blood glucose levels, suggesting that this extract might be its potent fraction (Chen et al., 1995). In addition, the hypoglycemic activity of the flavonoid-rich fraction of the 70% alcohol extract of the Egyptian *M. alba* root bark (MRBF-3) was evaluated after oral administration to STZ-induced diabetic rats. This treatment reduced the blood glucose concentration from 379 ± 9 mg/dl (control) to 155 ± 8 mg/dl, and significantly increased the INS level from 10.8 ± 0.3 μU/ml (control) to 15.6 ± 0.3 μU/ml (Singab et al., 2005). Furthermore, *M. nigra* bark extract decreased blood glucose levels in alloxan-diabetic mice (Hosseinzadeh et al., 1999). Much research has been done to observe the function of MCR in preventing the development of peripheral nervous lesions at the early stage of diabetes in rats. MCR could effectively enlarge the area of myelin sheath, extramedullary fiber and the cross-section of myelin sheath in alloxan–induced diabetes rats. It has been suggested that the protein tyrosine phosphatase 1B (PTP1B) inhibitor could be used to treat not only Type 2 diabetes but also obesity. In searches for PTP1B inhibitors from medicinal plants, an ethyl acetate-soluble extract of the root bark of *Morus* spp. an unspecified species of *Morus* was found to possess PTP1B
inhibition activity (63% inhibition at 30 μg/mL) (Cui et al, 2006).

**Mulberry Fruit**

The hypolipidemic and antioxidant effects of the freeze-dried powder of *M. alba* fruit (MFP) as a dietary supplement were evaluated in rats that were fed 4 weeks of either a high-fat or a normal diet supplemented with 5% or 10% MFP. Administration of MFP to rats on a high-fat diet resulted in significant decline in levels of serum and liver TG, TCH, serum LDL cholesterol, and a decrease in the atherogenic index, while serum HDL cholesterol was significantly increased. In addition, thiobarbituric acid-related substances in serum and liver and a lipid peroxidation product were significantly decreased, while the superoxide dismutase (SOD) of red blood cell and liver, as well as blood glutathione peroxidase (GSH-Px) activities were markedly increased (Yang et al, 2010). As for the ethyl acetate-soluble extract of mulberry fruit (MFE), MFE showed potent α-glucosidase inhibitory activity and radical-scavenging activities against DPPH and superoxide anion radicals *in vitro*. *In vivo*, MFE could significantly decrease fasting blood glucose (FBG) and glycosylated serum protein (GSP), and increase antioxidant enzymatic activities (SOD, CAT, GSH-Px) in ST-induced diabetic mice (Wang et al, 2013). It has been reported that *Fructus Mori* polysaccharide (FMP) could significantly reduce the levels of blood glucose, HbA1c, TG, TCH and LDL (*p* < 0.05), and improve the levels of HDL and INS (*p* < 0.05) compared with the model group (Tian et al, 2011). In addition, another research showed that the ethanolic extract of mulberry fruit (EMF) rapidly increased antioxidant activity in a concentration-dependent manner (Bae et al, 2007). The DPPH radical scavenging activity of methanol extract of mulberry fruits (MMF) was both concentration-dependent and correlated with total phenolic constituents (Imran et al, 2010).

**Other**

It has been reported that mulberry fruit, mulberry leaves and silkworm powder can improve antioxidant activity within our bodies. They can increase lipid metabolism in a diabetic liver and prevent diabetic complications (Kwon et al, 2006). In one study, rats were fed diets containing mulberry juice and mulberries for 3 weeks before the induction of diabetes by STZ. The experimental group exhibited lower blood glucose levels than rats in the control group. At the same time, rats that were fed mulberries showed lower serum cholesterol and TG levels than the control group (Kwon et al, 2007).
**Anti-diabetic Effects and Mechanisms of Specific Components from Mulberry**

Among the chemical constituents of mulberry, specific compounds have been reported to have anti-hyperglycemic activities, or to be associated with DM pathology, including polyhydroxylated alkaloids, flavonoids and polysaccharides. Different compounds may exert various effects on DM. Relevant experiments *in vitro, in vivo* on cells, on animals or on humans are detailed in the following sections (*Table 2*).

**Polyhydroxylated Alkaloids**

Alkaloids mimicking the structures of monosaccharides are now believed to be widespread in plants and microorganisms. These sugar mimics inhibit glycosidases because of a structural resemblance to the sugar moiety of the natural substrate (Asano *et al*, 2001). The total alkaloid fraction of mulberry leaf has showed strong inhibitory effects on intestinal saccharase, ($IC_{50} = 0.26 \mu g/ml$ for sucrase and $0.05 \mu g/ml$ for maltase) of rats, and this inhibitory effect ($0.69 \mu g/ml$) was stronger than the positive control acarbose ($0.75 \mu g/ml$) (Tao *et al*, 2010).

**DNJ**

In 1976, DNJ (1) has been isolated from the root bark of mulberry tree and called it moranoline (Yagi *et al*, 1976). Of all mulberry constituents, DNJ possesses the most potent $\alpha$-glucosidase inhibition, and it can lower blood glucose levels. Generally, DNJ content was found to be highest in trunk bark, whereas $\alpha$-glucosidase inhibitory activity was high in both twig and trunk bark. Buds and roots are likely to be the topmost and bottommost sites of DNJ (1) biosynthesis (Liu *et al*, 2014).

The glucose analog, DNJ, showed hypoglycemic activity which was associated with improvement of both INS secretion and INS sensitivity in diabetic animals (Huang *et al*, 2014). Also, DNJ greatly inhibited both partially purified oligosaccharide glucosidases from *S. cerevisiae* and the calf pancreas microdases which remove all other glucose residues (Saunier *et al*, 1982). In addition, DNJ (1) and two $N$-substituted derivatives instantaneously and completely inhibited the $\alpha$-1,6-glucosidase activity of the debranching enzyme, with $I_{50}$ values in the $\mu$molar range. In contrast, the glucanotransferase activity of the latter enzyme was not inhibited by the DNJ compounds at 0.2 mM. From this observation DNJ (1) emerged as a probable inhibitor of glycogenolysis (Bollen *et al*, 1989).
Meanwhile, DNJ (1) improved glucose consumption and enhanced intracellular glucokinase (GK) activities in HepG2 cells.

DNJ (1) treatment also showed strong antidiabetic effects in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, with improvement of fasting blood glucose levels, glucose tolerance, and, especially, INS sensitivity. Furthermore, there was substantial loss of body weight. DNJ (1) also showed significant anti-hyperglycemic effects in rats with diabetes induced by high fat diet and STZ. Its efficacy and dose profiles were better than those of acarbose (Kong et al, 2008). Others also observed that DNJ-rich MLE suppressed elevation of postprandial blood glucose in humans. Moreover, no adverse events associated with DNJ-rich MLE were observed after administration (Kojima et al, 2010).

Humans who consumed DNJ-enriched powder showed a decrease in plasma INS secretion compared to subjects taking a placebo. The suppression of both plasma glucose and INS is characteristic of an α-glucosidase inhibitor; therefore, DNJ in the mulberry powder might act as an intestinal α-glucosidase inhibitor (Kimura et al, 2007). In 2008, DNJ (1) has been assayed to determine whether it inhibited the activity of α-glucosidase from rat intestine (IC$_{50}$ is 1.5×10$^{-4}$ M) (Shibano et al, 2008).

**Fagomine**

1, 2-dideoxy nitrogen sugars are other important glycosidase inhibitors, and fagomine (3) is prominent among them. Fagomine (3) has been shown to act against mammalian gut α-glucosidase, but no other glycosidase inhibitory activity has been reported (Asano et al, 2003). It has been reported that the fagomine (3) -induced potentiation of INS release might partly contribute to anti-hyperglycemic action in STZ-diabetic mice (Nojima et al, 1998). Significantly, if fagomine (3) is used as a dietary supplement or functional food component it may reduce the risks of developing INS resistance, becoming over-weight and/or suffering from an excess growth of potentially pathogenic bacteria (Amézqueta et al, 2012). Another study showed that fagomine (3) reduced the amount of enterobacteria in feces of rats which were fed a high-fat high-sucrose diet; if it has a similar effect on humans, it could possibly help to prevent obesity (Ramos-Romero et al, 2014). In rat pancreatic islets, fagomine (3) (3 mM) potentiated 8.3 mM glucose-induced immunoreactive INS release from isolated perfused rat pancreas. The mechanism of anti-hyperglycemic effect by fagomine (3) may be due to
the potentiation of the INS (Kimura et al, 1995). It has been reported that more than 1 mmol/L fagomine (3) significantly potentiated INS secretion induced by 10 mmol/L glucose. Moreover, fagomine (3) (4 mmol/L) also strengthened glyceraldehyde-induced INS secretion (Taniguchi et al, 1998). However, it did not affect the basal INS secretion assessed at a glucose concentration of 3.5 mmol/L. For the derivatives of fagomine (3), isofagomine showed an IC$_{50}$ value of 0.7 μM compared to 200 μM for fagomine (3). In addition, isofagomine was able to prevent basal and glucagon-stimulated glycogen degradation in cultured hepatocytes with IC$_{50}$ values of 2-3 μM (Jakobsen et al, 2001).

Other Polyhydroxylated Alkaloids

1,4-dideoxy-1,4-imino-arabinitol (5) is a potent competitive inhibitor of endoplasmic reticulum (ER) α-glucosidase II involved in N-linked oligosaccharide processing with K$_i$ 9.7 μM, and it has been shown to be a good nonspecific inhibitor of intestinal isomaltase, which processes α-glucosidase II, Golgi α-mannosidases I and II, and porcine kidney trehalase. N-methyl-1-doexynojirimycin (2) and N-butyl-1-deoxynojirimycin inhibit α-glucosidase I much more strongly than DNJ (1) (Asano et al, 2001). It has been reported that GAL-DNJ (12) and fagomine (3) lowered blood glucose level in a dose-dependent manner 6 h after injection; ED$_{50}$ values with 95% confidence limits were 115.0 (96.8-136.7) μmol/kg and 142.4 (130.5-155.3) μmol/kg, respectively. The ED$_{50}$ values with 95% confidence limits were 41.0 (31.8-52.7) mg/kg for hot water extract and 33.9 (26.6-43.1) mg/kg for ethanol-insoluble extract from mulberry leaves.

Flavonoids

The anti-diabetic effects of flavonoids and related constituents found in mulberry species have also been described. A concentrated flavonoid fraction from the root bark of M. alba exerted protective effect on rat pancreatic β-cells against STZ (Singab et al, 2005). It has been reported that total flavonoids from mulberry tree leaf (FMT) exerted a hypoglycemic effect on diabetic rats by inhibition of disaccharidases (Yu et al, 2002). The beneficial effects of FMT on serum lipid levels were more significant at 12 h after FMT administration than that after 6 h. Similar effects were obtained from the rats who were fed a high-fat diet (Li et al, 2009a). Besides, FMT showed strong radical scavenging activities, inhibition of advanced glycation end product (AGE) formation, and strong inhibitory
effects on rats intestinal saccharase (Tao et al, 2010).

One study has demonstrated that mulberry leaves efficiently protect human red blood cells (RBCs) against free radical-induced oxidative damage. It also found that quercetin (19) and kaempferol (20) are the predominant antioxidants in mulberry leaves. Compared to other compounds, astragalin (22) had the greatest protective effect against 2, 2’-Azobis(2-amidinopropane) dihydrochloride (AAPH)-induced oxidative hemolysis and GSH depletion in RBCs (Choi et al, 2013). In the oxygen radical absorbance capacity (ORAC) assay, quercetin (19) had the highest peroxyl radical scavenging capacity and a similar hydroxyl radical scavenging capacity. Another report examined the hypoglycemic activity of rutin (23) at a dose of 25 mg/kg in a diabetic rat model (Hunyadi et al, 2012). In previous studies, it had been reported that isoquercitrin (21) inhibited the activity of \( \alpha \)-glucosidase inside rat intestine \( (IC_{50} \text{ is } 2.4 \times 10^{-4} \text{ M}) \). And isoquercitrin (21) was reported to have free radical-scavenging activity and superoxide radical-scavenging activity (Shibano et al, 2008). In yet another study, enzymatic kinetics measurements documented that quercetin (19) and rutin (23) are effective inhibitors against \( \alpha \)-glucosidase. Their \( IC_{50} \) values were 0.017 mmol/L and 0.196 mmol/L, compared with the \( IC_{50} \) (0.091 mmol/L) of acarbose (Li et al, 2009b).

Morusin (28) is an isoprenylated flavone, isolated from the root bark of \( M. \) alba; its structure has been identified (Figure 3) (Chi et al, 2001). It has been showed that morusin is present in all parts of the mulberry plant (Ma et al, 2013). The content of morusin is highest in root bark and second highest in branch bark. Morusin has been shown to inhibit superoxide anion formation stimulated with phorbol myristate acetate (PMA) inside rat neutrophils in a concentration-dependent manner (Fukai et al, 2003).

Q3MG (24), is a flavonol glycoside, mostly distributed in mulberry leaves, and it is predominantly responsible for the anti-oxidative activities of mulberry leaf. It has been reported that Q3MG (24) improves hyperglycemia in obese mice, and, in humans, can reduce oxidative stress in the liver after daily dietary intake (Katsube et al, 2010). They also mention that Q3MG (24) and rutin (23) are the predominant flavonol glycosides in mulberry leaves. In their study, Q3MG (24), rutin (23) and isoquercitrin (21) were identified as major LDL antioxidant compounds in 60% ethanol extracts of \( M. \) alba leaves; they inhibit human LDL oxidation induced by copper ion. This anti-oxidative character was determined on the basis of oxidation lag time and calculated as epigallocatechin 3-gallate equivalents (58.3 \( \mu \)mol of epigallocatechin 3-gallate (EGCG) equivalent/g

14
of dry weight) (Katsube et al, 2006). Another research reported that the atherosclerotic lesion area in Q3MG-treated mice was significantly reduced by 52% compared with control group (Enkhmaa et al, 2005). Bioassay-guided fractionation from Morus spp. root bark resulted in the isolation of sanggenon C (29), sanggenon G (30) and kuwanon L (31), all three are PTP1B inhibitors. (Cui et al, 2006).

**Polysaccharides**

Polysaccharides from M. alba leaves exert strong competitive inhibition of α-glucosidase. The total polysaccharides of M. alba leaves (TPM) increase glucose tolerance and glycogen content while lowering the glucose content in mice with alloxan-induced diabetes. TPM (100 mg/kg, i.p.) increased the blood INS level in normal rats (Chen et al, 1996). In addition, one report has showed that treatment with a mulberry leaf polysaccharide (MLPII) inhibited pancreatic islet cell apoptosis and ameliorated the INS secretory capacity of pancreatic β-cells in diabetic rats (Zhang et al, 2014).

**Others**

Besides the components of mulberry described above, there are others that can also have a significant impact on DM development. For example, moracin M (32). According to one previous research report, 10 mg/kg of chlorogenic acid (33) showed significant hypoglycaemic activity in rats with non-neonatal STZ-induced diabetes ( Hunyadi et al, 2012). Meanwhile, chlorogenic acid (33) extracted from mulberry fruits showed antioxidant potential as determined by 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) (0.75–1.25 mmol Trolox/g), DPPH (EC₅₀ from 48 μg/mL to 79 μg/mL) and reducing power assays (Arfan et al, 2012). Another study reported that mulberrofuran C (33) is a PTP1B inhibitor (Cui et al, 2006). One study demonstrated that cytidine (35), 2-(1', 2', 3', 4'-tetrahydroxy-butyl)-5-(2'', 3'', 4''-trihydroxy-butyl)-pyrazine (36) strongly inhibited α-glucosidase.

**Conclusions**

This review summarizes the conclusions of previous research studies of the various species and botanical plant parts of mulberry for the treatment of DM. Mulberry, in four different forms, is a common and widely-used medicinal material in traditional Chinese medicine. There are more than ten species of mulberry used medicinally throughout the world. From these parts and species, nearly
40 compounds have been reported, of which the majority are polyhydroxylated alkaloids, followed by flavonoids, with a few polysaccharides. The research studies have mainly summarized the effects of water and ethanol extracts of mulberry leaf, twig, root bark and fruit. In addition, they have investigated the activities of the main ingredients such as DNJ (1), fagomine and flavonoids. Evidence suggests that the anti-diabetic effects of mulberry extracts and/or components may be because many of those components act as α-glucosidase inhibitors. The water-soluble components of mulberry have been shown capable of playing a significant role in the prevention, control and treatment of DM.

Discussion and Prospects
Many research studies have reported on the phytochemical and pharmacological aspects of mulberry as an anti-diabetic drug. Firstly, mulberry grows in different areas and has various species. M. alba is one of the most common species of mulberry (Devi et al., 2013). In order to unify the resource and ensure the quality and quantity of active ingredients in mulberry, it is essential to standardize good agricultural practice (GAP) of mulberry. Compared to mulberry root bark, mulberry leaf and fruit are more sustainable resources. Based on this character, we believe that development of products and medicines from mulberry leaf and fruit shall be more environmentally friendly than development of those products and medicines originating from root bark. Furthermore, polyhydroxylated alkaloids, flavonoids and polysaccharides from mulberry have anti-diabetic effects. Polyhydroxylated alkaloids have the strongest hypoglycemic effect among these three. It has been reported that derivatives of polyhydroxylated alkaloids have been used for the treatment of DM, such as the methyl and ethyl derivatives of DNJ (1). These derivatives show stronger hypoglycemic activity than DNJ in sucrose- or starch-loaded rat models. Acarbose, miglitol are selected as potential α-glucosidase inhibitors (Asano et al., 2003). Currently, there are no perfect evaluation criteria for scientists to evaluate activities of α-glucosidase inhibitors of mulberry in vivo in term of hypoglycemic effect. More studies are needed in this respect to establish more convincing evaluation criteria. In clinical trials, mulberry has exhibited hypoglycemic and hypolipidemic effects in diabetic patients (Andallu et al., 2012). For further research, randomized, double-blind and controlled trials should be designed and implemented. Lastly, there have been no reports about the side effects or other negative factors of mulberry; therefore, we need to pay attention on this respect, and it deserves further study in the future.
Acknowledgements
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Abbreviations
AAPH, 2,2’-Azobis(2-amidinopropane) dihydrochloride; ABTS, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid); ALT, Alanine transaminase; AST, Aspartate transaminase; CAT, catalase; Cr, creatinine; COX-2, cyclooxygenase-2; DM, diabetes mellitus; DNJ, 1-deoxynojirimycin; DPPH, 1,1-diphenyl-2-picrylhydrazyl; EGCG, epigallocatechin 3-gallate; FBG, fasting blood glucose; FMT, flavonoids from mulberry tree leaf; GK, glucokinase; GSP, glycosylated serum protein; GST glutathione-S-transferase; GSH-px, glutathione peroxidase; GSH-Rd, glutathione reductase; G6PDH, glucose-6-phosphate dehydrogenase; HbA1c, hemoglobin A1c; HO-1 heme oxygenase-1; HDL, high density lipoprotein; IC50, 50% inhibition; IL-6/8, interleukin-6/8; INS, Insulin; LDL, low density lipoprotein; MCR, Mori Cortex Radicis; MDA, malonaldehyde; MnSOD, manganese superoxide dismutase; PDX-1, Pancreatic duodenal homeobox 1; PMA, phorbol myristate acetate; PTP1B, protein tyrosine phosphatase 1B; Q3MG, quercetin 3-(6-malonylglucoside); SD, Sprague-Dawley; SOD, superoxide dismutase; STZ, streptozotocin; TC, cholesterol; TCH, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; Trolox, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; VLDL, very low density lipoprotein.

References


Hunyadi, A., A. Martins, T. J. Hsieh, A. Seres and I. Zupkó. Chlorogenic acid and rutin play a major


Pharmacopoeia Committee of People’s Republic China, Pharmacopoeia of People’s Republic China, 2015.


Figure Legends

Figure 1  Fruiting branch of a mulberry plant

Figure 2  Chemical structures of polyhydroxylated alkaloids from mulberry

Figure 3  Chemical structures of flavonoids from mulberry

Figure 4  Chemical structures of other compounds from mulberry
Figure 1 Fruiting branch of a mulberry plant
Figure 2 Chemical structures of polyhydroxylated alkaloids from mulberry
Figure 3 Chemical structures of flavonoids from mulberry
**Figure 4** Chemical structures of other compounds from mulberry

(32) Moracin M

(33) Mulberrofuran C

(34) Chlorogenic acid

(35) Cytidine

(36) 2-(1', 2', 3', 4'-Tetrahydroxy-butyl) -5-(2'', 3'', 4''-trihydroxy-butyl) pyrazine
<table>
<thead>
<tr>
<th>Material</th>
<th>Animal/cell line</th>
<th>Dose/duration</th>
<th>Results and mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLP</td>
<td>Male mild type 2 diabetic patients</td>
<td>3 g/d, MLP, tid, p.o. for 30 days</td>
<td>Serum TCH, TG, plasma free fatty acids, LDL-cholesterol, VLDL-cholesterol, plasma peroxides, urinary peroxides↓, HDL-cholesterol↑</td>
<td>(Andallu et al, 2012)</td>
</tr>
<tr>
<td>LDL receptor-deficient (Ldlr^{−/−}) rats</td>
<td>Atherogenic diet + 3 g/100 g for 8 weeks</td>
<td>Atherosclerotic lesion area↓</td>
<td>(Li et al, 2011)</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein E-deficient mice</td>
<td>A diet containing 1% MLP for 12 weeks</td>
<td>→ lipoprotein oxidation; atherosclerotic lesion size↓; DPPH radical scavenging activity↑</td>
<td>(Harauma et al, 2007)</td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>12 and 18 mg + 50 g sucrose for 30-180 min</td>
<td>INS secretion↑; blood glucose↓</td>
<td>(Kimura et al, 2007)</td>
<td></td>
</tr>
<tr>
<td>MLP (Morus alba)</td>
<td>KK-Ay mice</td>
<td>0%, 3%, or 6% MLP containing high-sucrose diets for 8 weeks</td>
<td>FBG, urinary glucose excretion (3% and 6% MLP groups)↓, plasma INS (6% MLP group)↓</td>
<td>(Tanabe et al, 2011)</td>
</tr>
<tr>
<td>MLP (Morus indica)</td>
<td>Normal Wistar albino and STZ-induced diabetic rats</td>
<td>25% MLP of standard feed, p.o. for 8 weeks</td>
<td>→ Lipid peroxidation, CAT↑; FBG, vitamin C, vitamin E, G6PDH, GSH-px, SOD↓</td>
<td>(Bondada et al, 2014)</td>
</tr>
<tr>
<td>MLP</td>
<td>GK rats; Wistar rats</td>
<td>10%MLP, p.o. for 8 weeks</td>
<td>FBG, INS, C-reactive protein, and TG↓</td>
<td>(Park et al, 2009)</td>
</tr>
<tr>
<td>MLW</td>
<td>GK rats; Wistar rats</td>
<td>2 g/kg maltose + or - 3.75 g/kg MLE, p.o. for a week, then 2 g/kg glucose + or - 3.75 g/kg MLE, p.o. for 30 min</td>
<td>Blood glucose↓</td>
<td>(Park et al, 2009)</td>
</tr>
<tr>
<td>MLW</td>
<td>STZ-induced diabetic rats</td>
<td>100 and 200 mg/kg, \textit{i.p.}</td>
<td>Saliva secretion↑</td>
<td>(Chen \textit{et al}, 1995)</td>
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<tr>
<td>MLE</td>
<td>Male SD rats</td>
<td>1.87 g/kg, \textit{p.o.} 15 or 30 min</td>
<td>Glucose response↓</td>
<td>(Kwon \textit{et al}, 2011)</td>
</tr>
<tr>
<td></td>
<td>STZ-induced diabetic rats</td>
<td>1, 3, 10, and 30 mg/kg/day, \textit{i.g.} for 7 days</td>
<td>Water intake, FBG↓; body weight, INS secretion, INS sensitivity, glucose tolerance, kidney weight↑</td>
<td>(Huang \textit{et al}, 2014)</td>
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<tr>
<td>MLW</td>
<td>Diabetic rats</td>
<td>100, 200 and 400 mg/kg body weight, \textit{p.o.} for 21 days</td>
<td>HbA1c, serum and hepatic lipid peroxides↓; plasma INS, C-peptide, antioxidant enzymes, reduced glutathione, number of islets and β-cells of Langerhans↑</td>
<td>(Bala \textit{et al}, 2010)</td>
</tr>
<tr>
<td>MLE</td>
<td>STZ-diabetic rats</td>
<td>20 mg/100 g body weight, daily, \textit{p.o.} for 5 weeks</td>
<td>Food intake, blood glucose↓</td>
<td>(Ojewole \textit{et al}, 2006)</td>
</tr>
<tr>
<td>MLE</td>
<td>Diabetic rats</td>
<td>400 and 600 mg/kg body weight, \textit{i.p.} for 35 days</td>
<td>Blood glucose, HbA1c, TG, LDL, VLDL, blood urea, cholesterol↓; number of β-cells, and diameter of the islets of Langerhans↑</td>
<td>(Jamshid \textit{et al}, 2008)</td>
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<tr>
<td>MLE</td>
<td>STZ-induced diabetic rats</td>
<td>500 mg/kg/day, \textit{p.o.} for 10 days</td>
<td>Blood glucose↓; INS↑</td>
<td>(El-Mawla \textit{et al}, 2011)</td>
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<td>EMA</td>
<td>STZ-induced diabetic rats</td>
<td>200 mg/kg, \textit{i.p.} for 4 weeks</td>
<td>Blood glucose↓</td>
<td>(Chen \textit{et al}, 1995)</td>
</tr>
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<td>50% EMA</td>
<td>STZ-induced diabetic rats</td>
<td>0.25, 0.5 and 1 g/kg per day, \textit{p.o.} for 8 weeks</td>
<td>Blood glucose, blood pressure, acetylcholine and sodium nitroprusside↓; phenylephrine, malondialdehyde↓</td>
<td>(Naowaboot \textit{et al}, 2009)</td>
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<td>90% EMA</td>
<td>Diabetic rats</td>
<td>400 and 600 mg/kg, \textit{p.o.} for 5 weeks</td>
<td>Diameter of islets and number of β-cells↑; blood glucose↓</td>
<td>(Mohammadi \textit{et al}, 2012)</td>
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<tr>
<td>DNJ-rich MLE</td>
<td>Humans</td>
<td>12 mg three times daily before meals for 12 weeks</td>
<td>TG, CM-TG, VLDL↓; VLDL- TG, LDL, HDL↑</td>
<td>(Kojima \textit{et al}, 2010)</td>
</tr>
<tr>
<td><strong>HDP</strong> from mulberry leaves</td>
<td><strong>Alloxan-induced diabetic rats</strong></td>
<td><strong>150 mg/kg HDP, p.o. for 12 weeks</strong></td>
<td><strong>Body weight, pancreatic INS secretion, PDX-1, INS-1, INS-2, HDL, hepatic GCK mRNA↑; blood glucose, TG, HbA1c, ALT and AST, TC, LDL, PEPCK, G-6-Pase↓</strong> (Li et al, 2011)</td>
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<tr>
<td><strong>Mulberry tea</strong></td>
<td><strong>Caco-2 cell</strong></td>
<td><strong>10g/L, 0.2 mL mulberry tea infusion + 28 mM sucrose solution; or + 28 mM maltose solution</strong></td>
<td><strong>Liberated glucose contents↓</strong> (Hansawasdi et al, 2006)</td>
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<td><strong>Twigs</strong></td>
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<td><strong>BBE</strong></td>
<td><strong>STZ-induced diabetic mice</strong></td>
<td><strong>50, 100, and 200 mg/kg, p.o. for 3 weeks</strong></td>
<td><strong>Levels of serum INS, INS resistance↓; INS1, INS2, PDX-1↑</strong> (Liu et al, 2014)</td>
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<td><strong>RMP</strong></td>
<td><strong>STZ-induced diabetic rats</strong></td>
<td><strong>0.6 g/kg/d, p.o. for 14 days</strong></td>
<td><strong>Blood glucose, pathological lesions in pancreas tissue, TNF-α, IL-8, IL-6, COX-2, MDA↓; MnSOD, GSH-Rd, HO-1↑</strong> (Guo et al, 2013)</td>
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<td><strong>Root barks</strong></td>
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<td><strong>MRBF-3</strong></td>
<td><strong>STZ-induced diabetic rats</strong></td>
<td><strong>600 mg /kg/day, p.o. for 10 days</strong></td>
<td><strong>Blood glucose↓, INS↑</strong> (Singab et al, 2005)</td>
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<tr>
<td><strong>Mori Cortex extract</strong></td>
<td><strong>Alloxan-induced diabetes rats</strong></td>
<td><strong>1.875 g/kg, 0.625g/kg, i.g. for 2 months</strong></td>
<td><strong>Area of myelin sheath, extra-medullary fiber and the cross section of myelin sheath, body weight↑; myelin edema, lesion of sciatic nerve, FBG↓</strong> (Ma et al, 2013)</td>
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<td><strong>Fruits</strong></td>
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<tr>
<td>FMP</td>
<td>STZ-induced diabetic rats</td>
<td>150/300/450 mg/kg/d, <em>i.g.</em> for 60 d</td>
<td>Blood glucose, HbA1c, TG, TCH and LDL↓; HDL, INS↑</td>
<td>(Tian et al, 2011)</td>
</tr>
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<td>MFP</td>
<td>Wistar rats</td>
<td>high-fat or normal diet supplemented with 5% or 10% MFP, <em>p.o.</em> for 4 weeks</td>
<td>TG, TCH, LDL-cholesterol, atherogenic index, thiobarbituric acid related substances, lipid peroxidation product↓; HDL-cholesterol, SOD↑</td>
<td>(Yang et al, 2010)</td>
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<td>MFE</td>
<td>STZ-induced diabetic rats</td>
<td>100, 200 mg/kg BW; metformin, 300 mg/kg BW, <em>p.o.</em> two times a day for 2 weeks</td>
<td><em>In vitro</em>, === α-glucosidase; <em>In vivo</em>, FBG and GSP↓; SOD, CAT, GSH-Px↑</td>
<td>(Wang et al, 2013)</td>
</tr>
<tr>
<td>SFE</td>
<td>TEAC assay (Morus nigra and Morus alba)</td>
<td>48-79 μg/mL, 0.75-1.25 mM Trolox/g</td>
<td>DPPH radical scavenging activity, ABTS↑</td>
<td>(Arfan et al, 2012)</td>
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<td>EMF</td>
<td>DPPH assay</td>
<td>10-1200 μg</td>
<td>DPPH radical scavenging activity↑</td>
<td>(Bae et al, 2007)</td>
</tr>
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<td></td>
<td>TBA assay</td>
<td>2-40 mg</td>
<td>Hydroxyl scavenging ability↑</td>
<td></td>
</tr>
<tr>
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<td>NBT assay</td>
<td>0.059-0.119 mg</td>
<td>Superoxide anion scavenging activity↑</td>
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<tr>
<td>MMF</td>
<td>DPPH assay</td>
<td>20-100 μg</td>
<td>DPPH radical scavenging activity↑</td>
<td>(Imran et al, 2010)</td>
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</table>

*Note:* BBE, branch bark extract; EMA, extract of *M. alba*; DNJ, 1-deoxynojirimycin; HDP, hybrid of DNJ and polysaccharide; EMF, extract of mulberry fruit; FMP, Fructus Mori polysaccharide; MFE, ethyl acetate-soluble extract of mulberry fruit; MFP, powder of *M. alba* fruit; MLE, mulberry leaf extract; MLP, mulberry leaf powder; MLW, mulberry leaf water extract; MMF, methanol extract of mulberry fruits; NBT, nitroblue tetrazolium; RMP, Ramulus Mori polysaccharides; SFE, sugar-free extract of mulberry fruits; TBA, thiobarbituric acid; TEAC, Trolox equivalent antioxidant capacity; ===, inhibition; ↑, up-regulation; ↓, down-regulation.
<table>
<thead>
<tr>
<th>Material</th>
<th>Animal/cell line</th>
<th>Dose/duration</th>
<th>Results and mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNJ (1)</td>
<td><em>S. cerevisiae</em></td>
<td>20 μM; 2 μM</td>
<td>↓ oligosaccharide glucosidase</td>
<td>(Saunier et al, 1982)</td>
</tr>
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<td>Calf pancreas microsomes</td>
<td>2 μM</td>
<td>↓ oligosaccharide glucosidase</td>
<td>(Saunier et al, 1982)</td>
</tr>
<tr>
<td></td>
<td>IEC-6 rat intestinal epithelial cells</td>
<td>10 mM</td>
<td>↓ mannoside</td>
<td>(Saunier et al, 1982)</td>
</tr>
<tr>
<td></td>
<td>α-Glucosidase from rats intestine</td>
<td>150 μM</td>
<td>↓ α-glucosidase</td>
<td>(Shibano et al, 2008)</td>
</tr>
<tr>
<td></td>
<td>Hepatocytes from fed male Wistar rats</td>
<td>1 μM</td>
<td>↓ hepatic glycogenolysis</td>
<td>(Bollen et al, 1989)</td>
</tr>
<tr>
<td></td>
<td>OLETF rats</td>
<td>100 mg/kg, <em>p.o.</em></td>
<td>FBG, glucose tolerance, INS sensitivity↑; body weight↓</td>
<td>(Kong et al, 2008)</td>
</tr>
<tr>
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<td>Humans</td>
<td>12 mg three times daily before meals for 12 weeks</td>
<td>Serum TG, CM-TG, VLDL↓; VLDL-TG, LDL, HDL↑</td>
<td>(Kojima et al, 2010)</td>
</tr>
<tr>
<td></td>
<td>Humans</td>
<td>12 and 18 mg + 50 g sucrose for 30-180 min</td>
<td>INS secretion, blood glucose↓</td>
<td>(Kimura et al, 2007)</td>
</tr>
<tr>
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<td>STZ-induced diabetic rats</td>
<td>30 mg/kg/day, for 7 days</td>
<td>Water intake, food intake, FBG, blood pressure↓; body weight, INS secretion, glucose tolerance, kidney weight↑</td>
<td>(Huang et al, 2014)</td>
</tr>
<tr>
<td>Fagomine (3)</td>
<td>STZ-induced diabetic rats</td>
<td>300 µmol/kg, <em>i.p</em> for 2 h</td>
<td>Blood glucose↓</td>
<td>(Kimura et al, 1995)</td>
</tr>
<tr>
<td></td>
<td>STZ-induced diabetic rats</td>
<td>150 µmol/kg, <em>i.p.</em> for 2-6 h</td>
<td>Blood glucose↓, plasma INS release↑</td>
<td>(Nojima et al, 1998)</td>
</tr>
<tr>
<td></td>
<td>Sprague–Dawley rats</td>
<td>High-fat high-sucrose diet (HFHS) + 0.065% fagomine for 5 weeks</td>
<td>Proportions of enterobacteriales, weight↓</td>
<td>(Ramos-Romero et al, 2014)</td>
</tr>
<tr>
<td></td>
<td>Pancreatic islets</td>
<td>4 mM</td>
<td>INS secretion↑</td>
<td>(Taniguchi et al, 1998)</td>
</tr>
<tr>
<td>GAL-DNJ (12)</td>
<td>STZ-induced diabetic rats</td>
<td>300 µmol/kg <em>i.p.</em> for 4, 6 h</td>
<td>Blood glucose↓</td>
<td>(Kimura et al, 1995)</td>
</tr>
<tr>
<td>Quercetin (19)</td>
<td>Oxygen radical absorbance capacity assay</td>
<td>40 μL, 50 μM</td>
<td>Peroxyl radical-scavenging capacity↑; hydroxyl radical-scavenging capacity↑</td>
<td>(Kim et al, 2011)</td>
</tr>
<tr>
<td>Compound</td>
<td>Activity</td>
<td>Concentration</td>
<td>Source/Reference</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------</td>
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<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>HepG2 cells</td>
<td>AAPH- and Cu²⁺-induced oxidative stress↓</td>
<td>10 µM</td>
<td>(Kim et al, 2011)</td>
<td></td>
</tr>
<tr>
<td>Enzymatic kinetics measurements</td>
<td>0-200 µM</td>
<td>—→ α-glucosidase</td>
<td>(Li et al, 2009b)</td>
<td></td>
</tr>
<tr>
<td>Isoquercitrin (21)</td>
<td>SOD assay kit</td>
<td>53.9 µM</td>
<td>Superoxide radical-scavenging↑</td>
<td>(Shibano et al, 2008)</td>
</tr>
<tr>
<td>DPPH assay</td>
<td>DPPH radical-scavenging activity↑</td>
<td>13.4 µM</td>
<td>(Shibano et al, 2008)</td>
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</tr>
<tr>
<td>α-Glucosidase from rat intestine</td>
<td>—→ α-glucosidase</td>
<td>240 µM</td>
<td>(Shibano et al, 2008)</td>
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</tr>
<tr>
<td>Rutin (23)</td>
<td>Oxygen radical absorbance capacity assay</td>
<td>50 µM</td>
<td>Hydroxyl radical-scavenging capacity↑</td>
<td>(Kim et al, 2011)</td>
</tr>
<tr>
<td>Human volunteers</td>
<td>58.3 µmol of EGCG equivalent/g of dry weight</td>
<td>LDL antioxidant activity↑</td>
<td>(Katsube et al, 2006)</td>
<td></td>
</tr>
<tr>
<td>Enzymatic kinetics measurements</td>
<td>0-200 µM</td>
<td>—→ α-glucosidase</td>
<td>(Li et al, 2009b)</td>
<td></td>
</tr>
<tr>
<td>Type II diabetic rat</td>
<td>Blood glucose↓</td>
<td>10 mg/kg</td>
<td>(Hunyadi et al, 2012)</td>
<td></td>
</tr>
<tr>
<td>TEAC assay</td>
<td>DPPH radical scavenging activity, ABTS↑</td>
<td>48 µg/mL to 79 µg/mL</td>
<td>(Arfan et al, 2012)</td>
<td></td>
</tr>
<tr>
<td>Q3MG (24)</td>
<td>Male C57BL/6J mice feed with a high fat-diet</td>
<td>Blood glucose; oxidative stress↓; expression of glycolysis-related genes↑</td>
<td>(Katsube et al, 2010)</td>
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<tr>
<td>LDL receptor-deficient (Ldlr⁻/⁻) mice</td>
<td>Atherosclerotic lesion area↓</td>
<td>Atherogenic-diet + 0.05 g Q3MG/100 g, for 8 weeks</td>
<td>(Enkhma et al, 2005)</td>
<td></td>
</tr>
<tr>
<td>Human volunteers</td>
<td>LDL antioxidant activity↑</td>
<td>58.3 µmol of EGCG equivalent/g of dry weight</td>
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<td></td>
</tr>
<tr>
<td>Sanggenon C (29)</td>
<td>Colorimetry</td>
<td>1.6-16.9 µM</td>
<td>—→ PTP1B</td>
<td>(Cui et al, 2006)</td>
</tr>
<tr>
<td>Compound</td>
<td>Assay</td>
<td>Concentration Range</td>
<td>Effect</td>
<td>Reference</td>
</tr>
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<td>--------------------</td>
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<tr>
<td>Sanggenon G (30)</td>
<td>Colorimetry</td>
<td>1.6-16.9 μM</td>
<td>(\rightarrow) PTP1B</td>
<td>(Cui et al., 2006)</td>
</tr>
<tr>
<td>Kuwanon L (31)</td>
<td>Colorimetry</td>
<td>1.6-16.9 μM</td>
<td>(\rightarrow) PTP1B</td>
<td>(Cui et al., 2006)</td>
</tr>
<tr>
<td>Mulberrofuran C (33)</td>
<td>Colorimetry</td>
<td>1.6-16.9 μM</td>
<td>(\rightarrow) PTP1B</td>
<td>(Cui et al., 2006)</td>
</tr>
<tr>
<td>Mulberrofuran C (33)</td>
<td>Type II diabetic rats</td>
<td>10 mg/kg</td>
<td>Blood glucose ↓</td>
<td>(Hunyadi et al., 2012)</td>
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<tr>
<td>Mulberrofuran C (33)</td>
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<td>48 μg/mL to 79 μg/mL</td>
<td>DPPH radical scavenging activity, Blood glucose ↓</td>
<td>(Arfan et al., 2012)</td>
</tr>
</tbody>
</table>

Note: ABTS, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid); DPPT, 1,1-diphenyl-2-picrylhydrazyl; DNJ, 1-deoxyojirimycin; EGCG, epigallocatechin 3-gallate; FBG, fast blood glucose; GAL, 2-O-α-D-glucopyranosyl; INS, insulin; LDL, low density lipoprotein; OLETF, Otsuka Long-Evans Tokushima fatty; PTP1B, protein tyrosine phosphatase 1B; Q3MG, quercetin 3-(6-malonylglucoside); TEAC, Trolox equivalent antioxidant capacity; TG, triglycerides; VLDL, very low density lipoprotein; \(\rightarrow\), inhibition; \(\uparrow\), up-regulation; \(\downarrow\), down-regulation.