12-2018

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Link to published article: https://doi.org/10.1142/S0192415X1850088X

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 (25^{th} to 27^{th} 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-l-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 B_2) **(7)**, 1α,2β,3α,4β,6α-pentahydroxy-nor-tropane (calystegin C_1) **(8)**, l,4-dideoxy-l,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 (GAL-DNJ) **(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-*O*-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 from10.8 ± 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, HbAlc, 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 μg/ml for sucrase and 0.05 μg/ml for maltase) of rats, and this inhibitory effect (0.69 μg/ml) was stronger than the positive control acarbose (0.75 μg/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 α-glucosidase inhibition, and it can lower blood glucose levels. Generally, DNJ content was found to be highest in trunk bark, whereas α-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 α-1,6-glucosidase activity of the debranching enzyme, with I_{50} values in the μmolar 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 a*l, 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-l,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 α-glucosidase inside rat intestine (IC_{50} is 2.4×10^{-4} 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 α-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 μmol of epigallocatechin 3-gallate (EGCG) equivalent/g

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 (EC_{50} 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

This work was partially supported by the National Natural Science Foundation of China (81603381, 81673691), the Guangdong Natural Science Foundation (2014A030313766, 2016A030313008), the Science and Technology Planning Project of Guangdong Province (2015A020211039), and the Shenzhen Science and Technology Innovation Committee (JCYJ20160518094706544).

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 glutathinone-S-tranferase; 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.

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Figure Legends

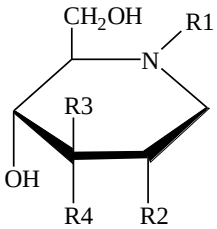
Figure 1 Fruiting branch of a mulberry plant

Figure 2 Chemical structures of polyhydroxylated alkaloids from mulberry

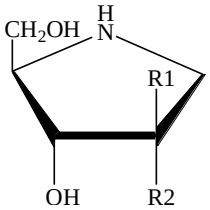
Figure 3 Chemical structures of flavonoids from mulberry

Figure 4 Chemical structures of other compounds from mulberry

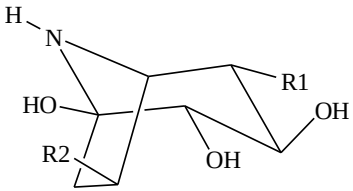
Figure 1 Fruiting branch of a mulberry plant



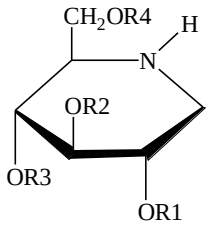
(1) R1=H R2=OH R3=OH R4=H
(2) R1=CH_3 R2=OH R3=OH R4=H
(3) R1=H R2=H R3=OH R4=H
(4) R1=H R2=H R3=H R4=OH



(5) R1=OH R2=H
(6) R1=H R2=OH
(9) R1=O-β-D-Glc R2=H
Glc=Glucopyranosyl

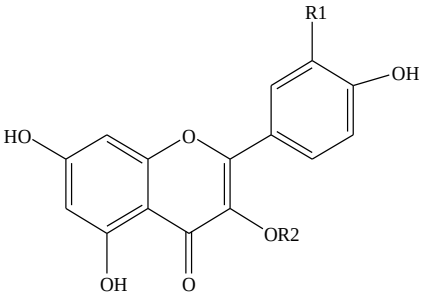


(7) R1=OH R2=H
(8) R1=OH R2=OH



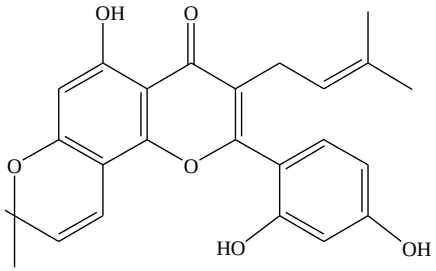
(10) R1=α-D-Gal R2=R3=R4=H
(11) R4=α-D-Gal R1=R2=R3=H
(12) R1=α-D-Glc R2=R3=R4=H
(13) R2=α-D-Glc R1=R3=R4=H
(14) R3=α-D-Glc R1=R2=R4=H
(15) R1=β-D-Glc R2=R3=R4=H
(16) R2=β-D-Glc R1=R3=R4=H
(17) R3=β-D-Glc R1=R2=R4=H
(18) R4=β-D-Glc R1=R2=R3=H
Glc=Glucopyranosyl Gal=Galactopyranosyl

Figure 2 Chemical structures of polyhydroxylated alkaloids from mulberry

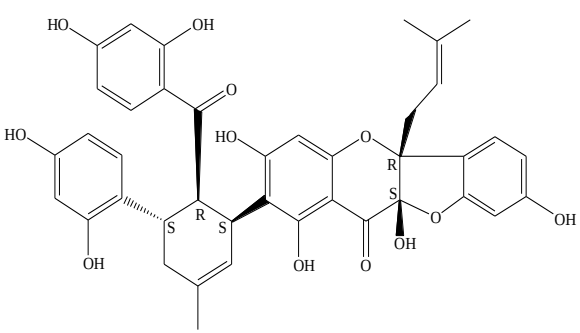


(19) R1=OH R2=H
(21) R1=OH R2=Glu
(23) R1=OH R2=Glu-Rha
(24) R1=OH R2=Glu-Mal
(25) R1=OH R2=Glu-Ac

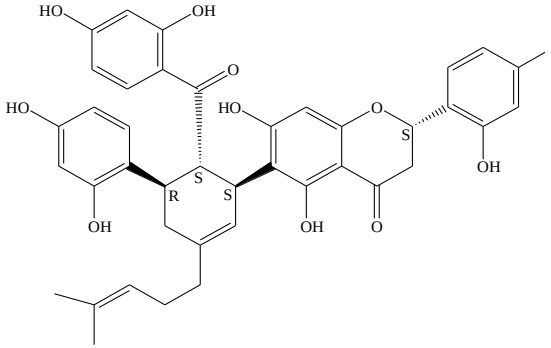
(20) R1=H R2=H
(22) R1=H R2=Glu
(26) R1=H R2=Glu-Rha
(27) R1=H R2=Glu-Mal



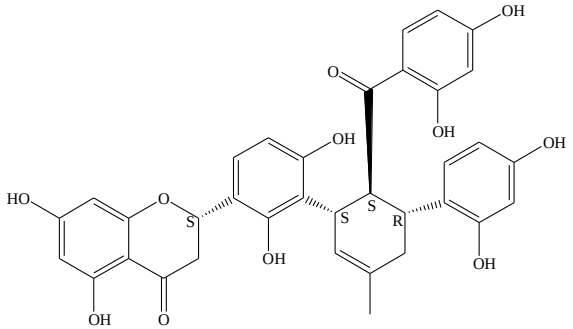
(28) Morusin



(29) Sanggenon C

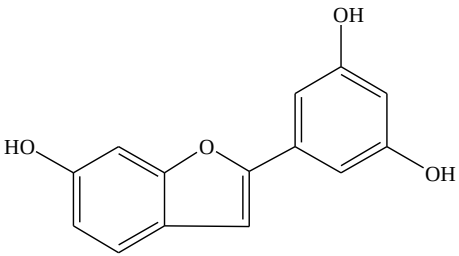


(30) Sanggenon G

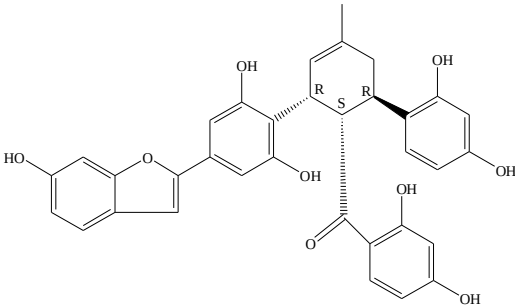


(31) Kuwanon L

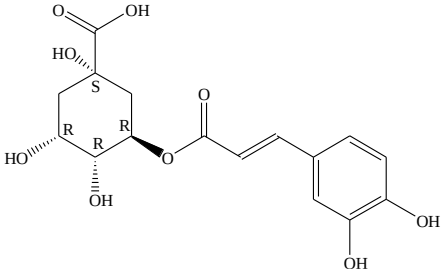
Figure 3 Chemical structures of flavonoids from mulberry



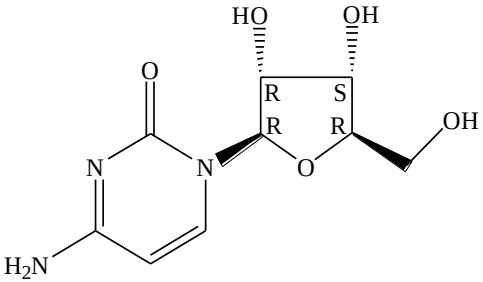
(32) Moracin M



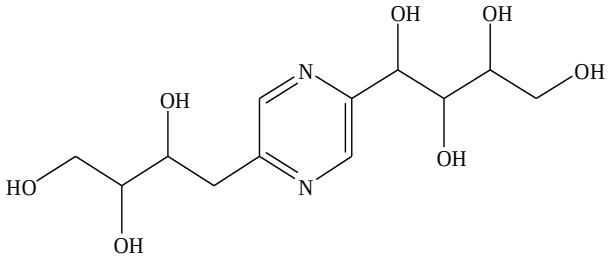
(33) Mulberrofuran C



(34) Chlorogenic acid



(35) Cytidine



(36) 2 - (l', 2', 3', 4'- Tetrahydroxy-butyl) -5- (2", 3", 4" - trihydroxy-butyl) pyrazine

Figure 4 Chemical structures of other compounds from mulberry

Table 1 Pharmacological effects of different medicinal parts of mulberry on diabetes

Material	Animal/cell line	Dose/duration	Results and mechanism	Ref.
Leaves				
MLP	Male mild type 2 diabetic patients	3 g/d, MLP, tid, *p.o*. for 30 days	Serum TCH, TG, plasma free fatty acids, LDL-cholesterol, VLDL-cholesterol, plasma peroxides, urinary peroxides↓, HDL-cholesterol↑	(Andallu *et al*, 2012)
	LDL receptor-deficient ($Ldlr^{-/-}$) rats	Atherogenic diet + 3 g/100 g for 8 weeks	Atherosclerotic lesion area↓	(Li *et al*, 2011)
	Apolipoprotein E-deficient mice	A diet containing 1% MLP for 12 weeks	⊣ lipoprotein oxidation; atherosclerotic lesion size↓; DPPH radical scavenging activity↑	(Harauma *et al*, 2007)
	Humans	12 and 18 mg + 50 g sucrose for 30-180 min	INS secretion↑; blood glucose↓	(Kimura *et al*, 2007)
MLP (*Morus alba*)	KK-Ay mice	0%, 3%, or 6% MLP containing high-sucrose diets for 8 weeks	FBG, urinary glucose excretion (3% and 6% MLP groups)↓, plasma INS (6% MLP group)↓	(Tanabe *et al*, 2011)
MLP (*Morus indica*)	Normal Wistar albino and STZ-induced diabetic rats	25% MLP of standard feed, *p.o.* for 8 weeks	⊣ Lipid peroxidation, CAT↑; FBG, vitamin C, vitamin E, G6PDH, GSH-px, SOD↓	(Bondada *et al*, 2014)
MLP	GK rats; Wistar rats	10%MLP, *p.o*. for 8 weeks	FBG, INS, C-reactive protein, and TG↓	(Park *et al*, 2009)
MLW	GK rats; Wistar rats	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	Blood glucose↓	(Park *et al*, 2009)

MLW	STZ-induced diabetic rats	100 and 200 mg/kg, *i.p*.	Saliva secretion↑	(Chen *et al*, 1995)
MLE	Male SD rats	1.87 g/kg, *p.o*. 15 or 30 min	Glucose response↓	(Kwon *et al*, 2011)
	STZ-induced diabetic rats	1, 3, 10, and 30 mg/kg/day, i.g. for 7 days	Water intake, FBG↓; body weight, INS secretion, INS sensitivity, glucose tolerance, kidney weight↑	(Huang *et al*, 2014)
MLW (*Morus rubra*)	Diabetic rats	100, 200 and 400 mg/kg body weight, daily, *p.o*. for 21 days	HbA1c, serum and hepatic lipid peroxides↓; plasma INS, C-peptide, antioxidant enzymes, reduced glutathione, number of islets and β-cells of Langerhans↑	(Bala *et al*, 2010)
MLE (*Morus alba*)	STZ-diabetic rats	20 mg/100 g body weight, daily, *p.o*. for 5 weeks	Food intake**,** blood glucose↓	(Ojewole *et al*, 2006)
	Diabetic rats	400 and 600 mg/kg body weight, *i.p*. for 35 days	Blood glucose, HbA1c, TG, LDL, VLDL, blood urea, cholesterol↓; number of β-cells, and diameter of the islets of Langerhans↑	(Jamshid *et al*, 2008)
MLE (*Morus nigra*)	STZ-induced diabetic rats	500 mg/kg/day, *p.o*. for 10 days	Blood glucose↓; INS↑	(El-Mawla *et al*, 2011)
EMA	STZ-induced diabetic rats	200 mg/kg, *i.p*. for 4 weeks	Blood glucose↓	(Chen *et al*, 1995)
50% EMA	STZ-induced diabetic rats	0.25, 0.5 and 1 g/kg per day, *p.o*. for 8 weeks	Blood glucose, blood pressure, acetylcholine and sodium nitroprusside↓; phenylephrine, malondialdehyde↓	(Naowaboot *et al*, 2009)
90% EMA	Diabetic rats	400 and 600 mg/kg, *p.o*. for 5 weeks	Diameter of islets and number of β-cells↑; blood glucose↓	(Mohammadi *et al*, 2012)
DNJ-rich MLE	Humans	12 mg three times daily before meals for 12 weeks	TG, CM-TG, VLDL↓; VLDL- TG, LDL, HDL↑	(Kojima *et al*, 2010)

HDP from mulberry leaves	Alloxan-induced diabetic rats	150 mg/kg ,HDP, *p.o*. for 12 weeks	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↓	(Li *et al*, 2011)
Mulberry tea	Caco-2 cell	10g/L, 0.2 mL mulberry tea infusion + 28 mM sucrose solution; or + 28 mM maltose solution	Liberated glucose contents↓	(Hansawasdi *et al*, 2006)
Twigs				
BBE	STZ-induced diabetic mice	50, 100, and 200 mg/kg,·*p.o*. for 3 weeks	Levels of serum INS, INS resistance↓; INS1, INS2, PDX-1↑	(Liu *et al*, 2014)
RMP	STZ-induced diabetic rats	0.6 g/kg/d, *p.o*. for 14 days	Blood glucose, pathological lesions in pancreas tissue, TNF-α, IL-8, IL-6, COX-2, MDA↓; MnSOD, GSH-Rd, HO-1↑	(Guo *et al*, 2013)
Root barks				
MRBF-3	STZ-induced diabetic rats	600 mg /kg/day, *p.o*. for 10 days	Blood glucose↓, INS↑	(Singab *et al*, 2005)
Mori Cortex extract	Alloxan-induced diabetes rats	1.875 g/kg, 0.625g/kg, *i.g*. for 2 months	Area of myelin sheath, extra-medullary fiber and the cross section of myelin sheath, body weight↑; myelin edema, lesion of sciatic nerve, FBG↓	(Ma *et al*, 2013)
Fruits				

FMP	STZ-induced diabetic rats	150/300/450 mg/kg/d, *i.g.* for 60 d	Blood glucose, HbA1c, TG, TCH and LDL↓; HDL, INS↑	(Tian *et al*, 2011)
MFP	Wistar rats	high-fat or normal diet supplemented with 5% or 10% MFP, *p.o*. for 4 weeks	TG, TCH, LDL-cholesterol, atherogenic index, thiobarbituric acid related substances, lipid peroxidation product↓; HDL-cholesterol, SOD↑	(Yang *et al*, 2010)
MFE	STZ-induced diabetic rats	100, 200 mg/kg BW; metformin, 300 mg/kg BW, *p.o*. two times a day for 2 weeks	*In vitro*, ⊣ α-glucosidase; *In vivo*, FBG and GSP↓; SOD, CAT, GSH-Px↑	(Wang *et al*, 2013)
SFE (*Morus nigra* and *Morus alba*)	TEAC assay	48-79 μg/mL, 0.75-1.25 mM Trolox/g	DPPH radical scavenging activity, ABTS↑	(Arfan *et al*, 2012)
EMF	DPPH assay TBA assay NBT assay	10-1200 μg 2-40 mg 0.059-0.119 mg	DPPH radical scavenging activity↑ Hydroxyl scavenging ability↑ Superoxide anion scavenging activity↑	(Bae *et al*, 2007)
MMF	DPPH assay	20-100 μg	DPPH radical scavenging activity↑	(Imran *et al*, 2010)

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 2 Pharmacological effects of typical components of mulberry on diabetes

Material	Animal/cell line	Dose/duration	Results and mechanism	Ref.
DNJ **(1)**	*S. cerevisiae*	20 μM; 2 μM	⊣ oligosaccharide glucosidase	(Saunier *et al*, 1982)
	Calf pancreas microsomes	2 μM	⊣ oligosaccharide glucosidase	(Saunier *et al*, 1982)
	IEC-6 rat intestinal epithelial cells	10 mM	⊣ mannose	(Saunier *et al*, 1982)
	α-Glucosidase from rats intestine	150 μM	⊣ α-glucosidase	(Shibano *et al*, 2008)
	Hepatocytes from fed male Wistar rats	1 μM	⊣ hepatic glycogenolysis	(Bollen *et al*, 1989)
	OLETF rats	100 mg/kg, *p.o*.	FBG, glucose tolerance, INS sensitivity↑; body weight↓	(Kong *et al*, 2008)
	Humans	12 mg three times daily before meals for 12 weeks	Serum TG, CM-TG, VLDL↓; VLDL-TG, LDL, HDL↑	(Kojima *et al*, 2010)
	Humans	12 and 18 mg + 50 g sucrose for 30-180 min	INS secretion, blood glucose↓	(Kimura *et al*, 2007)
	STZ-induced diabetic rats	30 mg/kg/day, for 7 days	Water intake, food intake, FBG, blood pressure↓; body weight, INS secretion, glucose tolerance, kidney weight↑	(Huang *et al*, 2014)
Fagomine **(3)**	STZ-induced diabetic rats	300 μmol/kg, *i.p* for 2 h	Blood glucose↓	(Kimura *et al*, 1995)
	STZ-induced diabetic rats	150 μmol/kg, *i.p*. for 2-6 h	Blood glucose↓, plasma INS release↑	(Nojima *et al*, 1998)
	Sprague–Dawley rats	High-fat high-sucrose diet (HFHS) + 0.065% fagomine for 5 weeks	Proportions of enterobacteriales, weight↓	(Ramos-Romero *et al*, 2014)
	Pancreatic islets	4 mM	INS secretion↑	(Taniguchi *et al*, 1998)
GAL-DNJ **(12)**	STZ-induced diabetic rats	300 μmol/kg *i.p* for 4, 6 h	Blood glucose↓	(Kimura *et al*, 1995)
Quercetin **(19)**	Oxygen radical absorbance capacity assay	40 μL, 50 μM	Peroxyl radical-scavenging capacity↑; hydroxyl radical-scavenging capacity↑	(Kim *et al*, 2011)

	HepG2 cells	10 μM	AAPH- and Cu^{2+}-induced oxidative stress↓	(Kim *et al*, 2011)
	Enzymatic kinetics measurements	0-200 μM	⊣ α-glucosidase	(Li *et al*, 2009b)
Isoquercitrin **(21)**	SOD assay kit	53.9 μM	Superoxide radical-scavenging↑	(Shibano *et al*, 2008)
	DPPH assay	13.4 μM	DPPH radical-scavenging activity↑	(Shibano *et al*, 2008)
	α-Glucosidase from rat intestine	240 μM	⊣ α-glucosidase	(Shibano *et al*, 2008)
Rutin **(23)**	Oxygen radical absorbance capacity assay	50 μM	Hydroxyl radical-scavenging capacity↑	(Kim *et al*, 2011)
	Human volunteers	58.3 μmol of EGCG equivalent/g of dry weight	LDL antioxidant activity↑	(Katsube *et al*, 2006)
	Enzymatic kinetics measurements	0-200 μM	⊣ α-glucosidase	(Li *et al*, 2009b)
	Type II diabetic rat	10 mg/kg	Blood glucose↓	(Hunyadi *et al*, 2012)
	TEAC assay	48 μg/mL to 79 μg/mL 0.75–1.25 mM Trolox/g	DPPH radical scavenging activity, ABTS↑	(Arfan *et al*, 2012)
Q3MG **(24)**	Male C57BL/6J mice feed with a high fat-diet	1 g/kg, *p.o.* for 8 weeks	Blood glucose, oxidative stress↓; expression of glycolysis-related genes↑	(Katsube *et al*, 2010)
	LDL receptor–deficient ($Ldlr^{-/-}$) mice	Atherogenic-diet + 0.05 g Q3MG/100 g, for 8 weeks	Atherosclerotic lesion area↓	(Enkhma *et al*, 2005)
	Human volunteers	58.3 μmol of EGCG equivalent/g of dry weight	LDL antioxidant activity↑	(Katsube *et al*, 2006)
Sanggenon C **(29)**	Colorimetry	1.6-16.9 μM	⊣ PTP1B	(Cui *et al*, 2006)

Sanggenon G **(30)**	Colorimetry	1.6-16.9 μM	⊣ PTP1B	(Cui *et al*, 2006)
Kuwanon L **(31)**	Colorimetry	1.6-16.9 μM	⊣ PTP1B	(Cui *et al*, 2006)
Mulberrofuran C **(33)**	Colorimetry	1.6-16.9 μM	⊣ PTP1B	(Cui *et al*, 2006)
	Type II diabetic rats	10 mg/kg	Blood glucose↓	(Hunyadi *et al*, 2012)
Chlorogenic acid **(34)**	TEAC assay	48 μg/mL to 79 μg/mL 0.75–1.25 mM Trolox/g	DPPH radical scavenging activity, ABTS↑	(Arfan *et al*, 2012)

Note: ABTS, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid); DPPT, 1,1-diphenyl-2-picrylhydrazyl; DNJ, 1-deoxynojirimycin; 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; ⊣, inhibition; ↑, up-regulation; ↓, down-regulation.