

Alleviating Effects of Mulberry Fruit Extract on Postprandial Hyperglycemia in Streptozotocin-induced Diabetic Mice

Kyung Ha Choi^{1,2}, Ji-Hye Kang¹ and Ji-Sook Han^{1*}

¹Department of Food Science and Nutrition, and Research Institute of Ecology for the Elderly, Pusan National University, Busan 609-735, Korea

²Department of Food and Nutrition, College of Medical and Life Science, Silla University, Busan 616-735, Korea

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Postprandial hyperglycemia is an early defect of type 2 diabetes and one of primary anti-diabetic targets. The alpha-glucosidase inhibitors regulate postprandial hyperglycemia by impeding the rate of carbohydrate (such as starch) digestion in the small intestine. This study was designed to investigate the inhibitory actions of mulberry fruit extract (MFE) on α -glucosidase and α -amylase activities, and its alleviating effect on postprandial hyperglycemia activities in vitro and in vivo. Male four-week old ICR mice and streptozotocin (STZ)-induced diabetic mice were treated with mulberry fruit extract. MFE showed strong inhibitory effects against α -glucosidase and α -amylase activities, with half-maximal inhibitory concentration (IC_{50}) values of 0.16 and 0.14 mg/ml, respectively, and was more effective than acarbose, which was used as a positive control. The increase in postprandial blood glucose levels was more significantly attenuated in the MFE-administered group mice than in the control group mice of both STZ-induced diabetic and normal mice. Moreover, the area under the glucose response curve significantly decreased following MFE administration in diabetic mice. These results indicate that MFE may be a potent inhibitor of α -glucosidase and α -amylase, and helpful in suppressing postprandial hyperglycemia in diabetic mice. The mulberry fruit extracts may be considered as a potential candidate for the management of diabetes.

Key words : α -Amylase, α -Glucosidase, diabetic mice, mulberry fruit extract, postprandial hyperglycemia

Introduction

The prevalence of diabetes mellitus, a metabolic disease characterized by hyperglycemia resulting from defects in both regulations of insulin secretion and/or insulin action, is increasing worldwide [9]. The possibility that postprandial hyperglycemia is associated with the development of diabetic complications has recently received much attention [30]. An acute hyperglycemia after a meal may result in endothelial dysfunction and oxidative stress [11]. Moreover, studies have shown an association between postprandial glucose levels and the pathogenesis of atherosclerosis [32]. Therefore, management of postprandial hyperglycemia is considered a major therapeutic strategy for type 2 diabetes treatment, and can be achieved by delaying the release of glucose through the inhibition of carbohydrate hydrolyzing

enzymes such as α -amylase and α -glucosidase in the digestive tract [26].

α -glucosidase inhibitors such as acarbose and miglitol are hypoglycemic agents that slow the digestion and absorption of carbohydrates in the small intestine and hence, reduce the increase in blood glucose levels after a meal. However, it is well acknowledged that administration of such drugs is frequently associated with adverse effects including flatulence, abdominal pain, and diarrhea [5, 29]. Thus, many natural products having minimal side effects have been investigated with respect to their inhibition of glucose production from carbohydrates in the gut or glucose absorption from the intestine [3].

Mulberry (*Morus alba* L.) is a genus of flowering plants in the family Moraceae, and its fruits and leaves have been used as traditional oriental medicines to treat diabetes [4]. The mulberry fruit, called Oddi in Korea, is a 2- to 3 cm long multiple fruit. Immature fruits are white, green, or pale yellow. The fruits turn pink and then red while ripening, and finally dark purple or black with a sweet flavor when fully ripe. Mulberry fruits contain large amounts of anthocyanins. Cyanidin-3-glucoside (C3G) and cyanidin-3-rutinoside (C3R) are the most important active components of mul-

*Corresponding author

Tel : +82-51-510-2836, Fax : +82-51-583-3648

E-mail : hanjs@pusan.ac.kr

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berry, having many potentially beneficial effects on human health [22]. According to traditional oriental medicine, mulberry fruit can protect the liver and kidney from damage, strengthen the joints, improve eyesight, and possess anti-aging effects [21]. Furthermore, recent studies have demonstrated that mulberry fruit exhibits inhibitory effects on CYP3A activity [12], as well as neuroprotective [10], immunomodulatory [18], anti-inflammatory [19], hypolipidemic, and antioxidant properties [35].

However, no information is currently available about the inhibitory effect of mulberry fruits on intestinal α -glucosidase, either *in vitro* or *in vivo*. Therefore, we investigated whether mulberry fruit extracts may inhibit α -glucosidase and α -amylase activities, and alleviate postprandial hyperglycemia in streptozotocin (STZ)-induced diabetic mice.

Materials and Methods

Materials

Mulberry (*M. alba* L.) fruits were collected from the coast of Sangju-si Gyeongsangbuk-do, South Korea. The fruits were individually washed with tap water, rinsed carefully with fresh water, and freeze-dried. The dried sample was ground and sifted through a 50 mesh standard testing sieve. The sample was extracted three times with ten volumes of 80% methanol for 12 hr at room temperature. The filtrate was then vacuum-evaporated to obtain the extract. After the mulberry fruit extract (MFE) was thoroughly dried, it was stored in a deep freezer (-80°C). The composition of anthocyanins in the MFE was analyzed by high-performance liquid chromatography (HPLC), and C3G and C3R were found to be the major anthocyanins. The levels of C3G and C3R in the MFE were 34.1 and 14.3 mg/1.5 g, respectively [4].

Inhibition assay for α -glucosidase activity *in vitro*

The α -glucosidase inhibition assay was conducted by the chromogenic method described by Watanabe et al. (1997) using a readily available yeast enzyme [33]. Briefly, yeast α -glucosidase (0.7 units, Sigma, St. Louis, MO, USA) was dissolved in 100 mM phosphate buffer (pH 7.0) containing 2 g/l bovine serum albumin and 0.2 g/l NaN_3 to form the enzyme solution. The substrate solution was prepared by dissolving p-nitrophenyl- α -D-glucopyranoside (5 mM) in the same buffer. Next, 50 μ l of enzyme solution and 10 μ l of sample dissolved in dimethyl sulfoxide (5 mg/ml) were mixed in a well of a microtiter plate and the absorbance

at 405 nm was measured with a microplate reader at time zero. After incubation for 5 min, the substrate solution (50 μ l) was added and the mixture was incubated for another 5 min at room temperature. The increase in absorbance from time zero was measured. The inhibitory activity of MFE at varying concentrations was expressed as 100 minus the absorbance change of test compounds relative to the absorbance change of the control (%), where the test solution was replaced by the carrier solvent. The measurements were performed in triplicate and the IC_{50} value (the concentration of MFE that results in 50% inhibition of maximal activity) was determined.

Inhibition assay for α -amylase activity *in vitro*

The α -amylase inhibition assay was performed in the same way as described for the α -glucosidase inhibition assay except that porcine pancreatic amylase (100 units, Sigma) and p-nitrophenyl- α -D-maltopentoglycoside were used as the enzyme and substrate, respectively.

Experimental animals

Four-week-old, male ICR mice (Orient Bio Inc., Seongnam, Korea) were used as test animals and were housed individually in a light (12 hr on/12 hr off) and temperature-controlled room with *ad libitum* access to pelleted food and water. After a 2-week adjustment period, diabetes was induced as described below. All procedures were approved by the animal ethics committee of our university. All animal experiments were treated in accordance with guidelines of the Pusan National University for the care and use of laboratory animals (ED-PNU2014-0663).

Induction of diabetes

To induce diabetes, mice were fasted for 18 hr before administration of a single intraperitoneal (i.p.) injection of 60 mg/kg STZ prepared in 0.1 M sodium citrate buffer (pH 4.5). One week after injection of STZ, fasting blood glucose levels were periodically measured using a glucometer (Roche Diagnostics GmbH, Mannheim, Germany). Mice with blood glucose values of 250 mg/dl or higher were considered diabetic.

Measurement of blood glucose level

Normal mice and STZ-induced diabetic mice fasted overnight (deprived of food for at least 12 hr but allowed free access to water) were each randomly divided into 3 groups

of 7 mice (a total 6 groups) and treated as follows: 1) control: mice received oral administration of soluble starch (2 g/kg body weight [BW]) alone; 2) MFE: mice received oral administration of starch with MFE (300 mg/kg BW); 3) acarbose: mice received oral administration of starch with acarbose (100 mg/kg BW). Blood samples were taken from the tail vein at 0, 30, 60, and 120 min after oral administration. Blood glucose level was measured using a glucometer (Roche Diagnostics GmbH) and the area under the glucose response curve (AUC) was calculated using the trapezoidal rule [13].

Data and statistical analysis

The data are represented as the mean ± standard deviation (SD) of triplicate experiments. The statistical analysis was performed using SAS software ver. 9.1 (SAS Institute Inc., Cary, NC, USA). Differences among groups were evaluated by one-way analysis of variance (ANOVA) followed by Duncan’s multiple range test. Differences between two groups were compared using Student’s *t*-test. Values of *p* less than 0.05 were considered statistically significant.

Results and Discussion

Inhibitory effect of MFE on α-glucosidase and α-amylase *in vitro*

The inhibitory effect of MFE against α-glucosidase was determined using p-nitrophenyl-α-glucopyranoside as the substrate. α-glucosidase activity was inhibited by MFE in a dose-dependent manner, with 28.57, 38.10, 48.15, and 59.26% inhibition at MFE concentrations of 0.05, 0.10, 0.15, and 0.20 mg/ml, respectively (Fig. 1). The α-glucosidase inhibitory activity of the MFE was significantly higher than that of the positive control, acarbose. The α-amylase inhibitory activity of MFE on the other hand, was determined using p-nitrophenyl-α-maltopentoglycoside as the substrate. Similarly, the inhibitory activity of MFE against α-amylase was also dose-dependent (34.52, 40.74, 53.70, and 61.57% inhibition at MFE concentrations of 0.05, 0.10, 0.15, and 0.20 mg/ml, respectively) (Fig. 2). Compared with the commercial inhibitor, acarbose, MFE was more effective in inhibiting α-amylase activity. The IC₅₀ values of MFE against α-glucosidase and α-amylase were 0.16 and 0.14 mg/ml, respectively, which demonstrated its stronger inhibitory activities over those of acarbose (Table 1).

Postprandial hyperglycemia is a prominent and early defect in the development of diabetes and an important factor

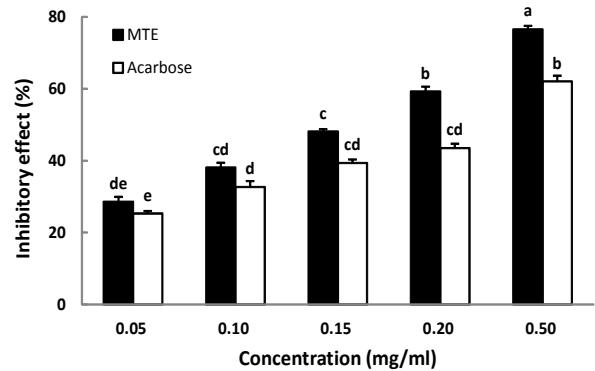


Fig. 1. Inhibitory effect of mulberry fruit extract (MFE) on α-glucosidase. Each value represents the mean ± SD of triplicate experiments. ^{a-e}Values denoted by different letters are significantly different at *p*<0.05 as analyzed by Duncan’s multiple range test. Acarbose was used as positive control.

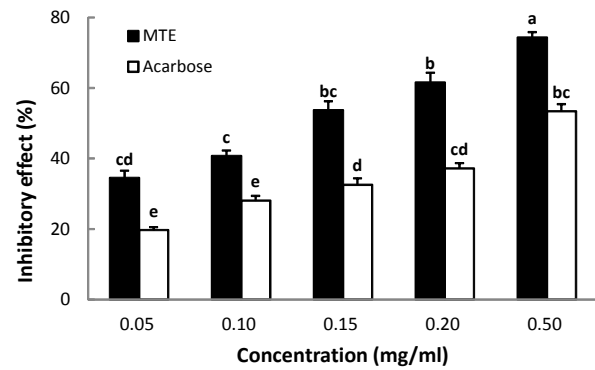


Fig. 2. Inhibitory effect of mulberry fruit extract (MFE) on α-amylase. Each value represents the mean ± SD of triplicate experiments. ^{a-e}Values denoted by different letters are significantly different at *p*<0.05 as analyzed by Duncan’s multiple range test. Acarbose was used as positive control.

Table 1. IC₅₀ values of the inhibitory effect of MFE on α-glucosidase and α-amylase

Sample	IC ₅₀ (mg/ml) ¹⁾	
	α-glucosidase	α-amylase
MFE	0.16±0.01*	0.14±0.01*
Acarbose	0.34±0.02	0.45±0.04

¹⁾IC₅₀ value is the concentration of sample required for 50% inhibition. Each value represents the mean ± SD of triplicate experiments.

* *p*<0.05 compared to the control group.

that contributes to complications associated with diabetes, such as micro- and macrovascular diseases. Therefore, alleviating hyperglycemia in the postprandial state is a treatment goal for patients with diabetes [27]. Starch is primarily di-

gested in the small intestine through the action of pancreatic α -amylase, producing both linear maltose and branched isomaltose oligosaccharides, which are further hydrolyzed by intestinal α -glucosidase to yield absorbable monosaccharides [17]. α -glucosidase catalyzes the final step in the digestive process of carbohydrates; hence, its inhibitors could impede the absorption of dietary carbohydrates to reduce postprandial hyperglycemia [24]. Thus, controlling postprandial hyperglycemia by inhibiting α -glucosidase and α -amylase is one of the key goals in diabetic therapy [1].

In the present study, the inhibitory activities of MFE on α -glucosidase and α -amylase were investigated to examine the possible use of MFE as an anti-hyperglycemic functional food. MFE has higher inhibitory activities on the aforementioned enzymes than the commercial carbohydrate digestive enzyme inhibitor, acarbose; and this can be attributed to the active compounds present in MFE. Mulberry fruits contain abundant anthocyanins, particularly C3G, C3R, pelargonidin 3-O-glucoside, and pelargonidin 3-O-rutinoside [20, 25].

These anthocyanins, belonging to the flavonoid class of polyphenolic compounds, are known to bind to a variety of proteins. The hydroxyl groups in polyphenolic compounds may link and form complexes with enzymes, thus inhibiting their activity [14, 31]. McDougall et al. [23] reported that anthocyanins from berry extracts have been implicated in the inhibition of α -glucosidase [23]. Furthermore, Iwai et al. [8] demonstrated that C3G contained in mulberry fruit significantly inhibited the activities of carbohydrases such as sucrose, α -glucosidase, and α -amylase [8]. Thus, we assume that MFE may possess similar inhibitory effects on α -glucosidase and α -amylase owing to the presence of these anthocyanins.

Effect of MFE on blood glucose level *in vivo*

The effect of MFE on postprandial blood glucose levels was determined in STZ-induced diabetic and normal mice. In diabetic mice, postprandial blood glucose levels of the MFE-administered group were lower than those of the control were (Fig. 3). Blood glucose levels of the control group increased to 402.5 mg/dl at 60 min after starch loading, before decreasing to 379.67 mg/dl at 120 min. On the other hand, postprandial blood glucose levels were noticeably lower ($p < 0.05$) when diabetic mice were fed with MFE (351.0, 369.7, and 352.0 mg/dl at 30, 60, and 120 min, respectively). Similarly in normal mice, MFE significantly reduced ($p < 0.05$)

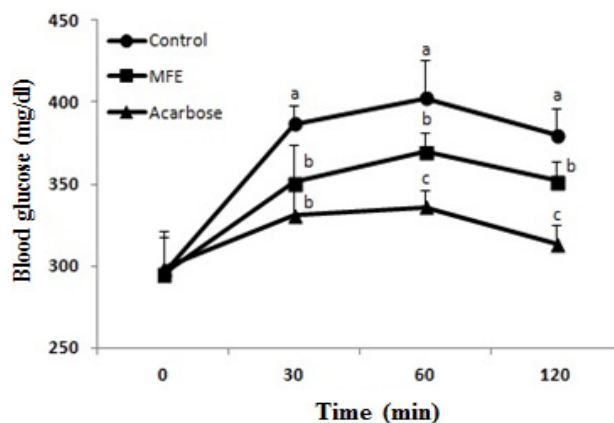


Fig. 3. Blood glucose levels after the administration of mulberry fruit extract (MFE) in STZ-induced diabetic mice. Distilled water (as control), MFE (300 mg/kg), and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). Each value represents the mean \pm SD of seven mice ($n = 21$). ^{a-c}Values denoted by different letters are significantly different at $p < 0.05$ as analyzed by Duncan's multiple range test.

postprandial hyperglycemia where the increase in postprandial blood glucose level was suppressed to 137.6, 129.2, and 112.6 mg/dl at 30, 60, and 120 min, respectively (Fig. 4). In diabetic mice, the AUC of glucose response was significantly lower in the MFE-administrated group (3330.2 ± 462.79 mmol \cdot min \cdot L $^{-1}$) than in the control group (5036.5 ± 289.6 mmol \cdot min \cdot L $^{-1}$) (Table 2), further supporting the hypoglycemic effect of MFE.

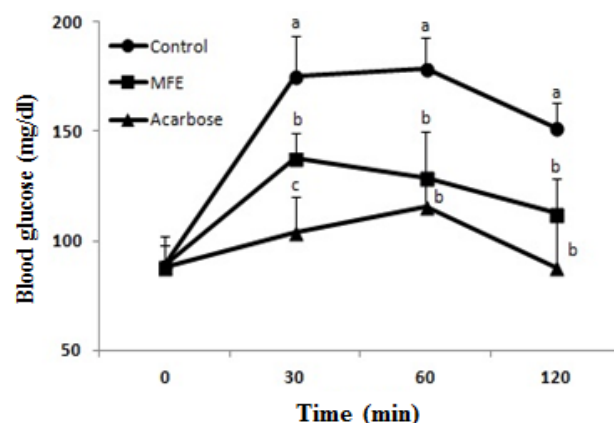


Fig. 4. Blood glucose levels after the administration of mulberry fruit extract (MFE) in normal mice. Distilled water (as control), MFE (300 mg/kg), and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). Each value represents the mean \pm SD of seven mice ($n = 21$). ^{a-c}Values denoted by different letters are significantly different at $p < 0.05$ as analyzed by Duncan's multiple range test.

Table 2. Area under the curve (AUC) of postprandial glucose responses of normal and streptozotocin-induced diabetic mice

Group ¹	AUC (mmol·min·L ⁻¹)	
	Normal mice	Diabetic mice
MFE	2586.0±576.6 ^b	3330.2±462.8 ^b
Acarbose	1703.7±51.3 ^c	2222.1±572.4 ^c
Control	4746.5±275.4 ^a	5036.5±289.6 ^a

¹MFE (300 mg/kg), acarbose (100 mg/kg), and distilled water (as control) were co-administered orally with starch (2 g/kg). Each value represents the mean ± SD of 7 mice (n = 42).

^{a-c}Values denoted by different letters are significantly different at $p < 0.05$ as analyzed by Duncan's multiple range test.

In diabetes, the postprandial phase is typified by a rapid and large increase in blood glucose levels, and the possibility that these postprandial "hyperglycemic spikes" may have a negative influence on the pathophysiology of late diabetes complications has recently received much attention [30]. Postprandial hyperglycemia reduces not only insulin secretion due to the dysfunction of the pancreas [2] but also insulin sensitivity [15, 16], resulting in a deteriorated diabetic state and late diabetes complications. Therefore, maintaining near-normal levels of glycemic control, both in the fasting and postprandial states, is a treatment goal for patients with type 2 diabetes [27]. In this study, we investigated the anti-hyperglycemic effects of MFE in STZ-induced diabetic mice and normal mice after the consumption of starch together with MFE. Postprandial blood glucose levels were significantly decreased in STZ-induced diabetic mice. Consistent with these findings, Ritta et al. [28] reported that dietary anthocyanins in berries significantly reduced postprandial glucose levels. Therefore, the results of our study suggest that anthocyanin contained in MFE may delay the absorption of dietary starch, thus attenuating the increase in postprandial blood glucose levels. This alleviating effect on postprandial hyperglycemia may be due to the inhibition of carbohydrate digestive enzymes in the small intestine of diabetic mice. Inone et al. (1997) showed that medication that flattens the peak of the postprandial blood glucose levels reduces the AUC of the blood glucose response curve [7]. In this study, MFE significantly decreased blood glucose level at the peak time point and hence, the AUC.

Diabetes is caused by alterations in carbohydrate metabolism leading to resistance to insulin secretion, thus resulting in a state of hyperglycemia [34, 36]. Postprandial hyperglycemia plays an important role not only in the develop-

ment of type 2 diabetes but also in complications associated with the condition, including microvascular and macrovascular diseases [2]. A large number of intervention trials have demonstrated that improving hyperglycemia achieves considerable reduction of these complications [6]. Although many synthetic compounds such as gliclazide, metformin, and voglibose have been used in the treatment of diabetes, they have in general been associated with marked toxic or undesirable side effects [5]. Therefore, mulberry fruit, containing abundant anthocyanins, may possibly be an excellent source of natural anti-diabetic agents. Our current findings suggest that MFE could potentially be developed as a natural functional food to improve postprandial hyperglycemia and prevent diabetic complications.

In conclusion, MFE inhibited α -glucosidase and α -amylase activities and attenuated the rise in blood glucose levels, leading to a reduction in postprandial hyperglycemia. Moreover, MFE may delay the absorption of dietary carbohydrates in the gut, hence suppressing the increase in blood glucose levels after a meal. Thus, MFE may be a useful food source to control diabetes and helpful in improving postprandial hyperglycemia.

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초록 : STZ으로 유도된 당뇨 마우스에서 오디열매추출물의 식후 고혈당 완화 효과최경하^{1,2} · 강지혜¹ · 한지숙^{1*}(¹부산대학교 식품영양학과, ²신라대학교 식품영양학과)

식후 고혈당은 제2형 당뇨병 초기 진단과 항당뇨병의 중요한 바이오마커 중 하나이다. α -글루코시다아제 억제제는 소장에서 탄수화물 소화의 속도를 방해함으로써 식후 고혈당을 조절한다. 본 연구에서는 오디열매추출물이 α -글루코시다아제와 α -아밀라아제에 미치는 억제효과 및 스트렙토조토신(STZ)이 유발하는 당뇨병 생쥐의 식후고혈당에 미치는 완화 효과를 조사하였다. α -글루코시다아제와 α -아밀라아제에 대한 오디열매추출물(MFE)의 IC_{50} 값은 각각 0.16과 0.14 mg/ml의 결과값을 나타내어, 양성대조군인 acarbose보다 더 효과적이었다. STZ으로 유발된 당뇨병 흰쥐의 식후 혈당 수치는 정상 대조군에 비해 오디열매추출물에서 유의적으로 더 낮았다. 더욱이, 오디열매추출물 투여는 당뇨병 흰쥐에서 포도당 반응에 대한 곡선하면적 감소와 관련이 있었다. 결론적으로, 오디열매추출물은 α -글루코시다아제와 α -아밀라아제 활성의 강력한 억제제이며 식후 고혈당을 완화할 수 있다는 내용이다. 따라서 오디열매추출물은 당뇨병 치료제 및 기능성식품의 소재로 가치가 높다고 사료된다.