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Development of Mulberry Leaf Extract for Suppressing Postprandial Blood Glucose Elevation

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1. Introduction

Epidemiological evidence indicates that postprandial hyperglycemia is an independent risk factor for cardiovascular disease (Bonora & Muggeo, 2001). Improving postprandial glycemic control is considered a target for decreasing the morbidity and mortality due to cardiovascular disease in prediabetic and diabetic individuals. Recently, clinical trials such as the STOP-NIDDM Trial and Victory Study demonstrated that α-glucosidase inhibitors (αGIs) reduced the progression from impaired glucose tolerance (IGT) to type 2 diabetes (Chiasson et al., 2002, 2003; Kawamori et al., 2009). Therefore, considerable attention has been paid to αGIs as preventive and therapeutic agents for type 2 diabetes and its complications. Some food consumed on a daily basis also contains αGIs and may therefore be effective for attenuating increase in postprandial blood glucose levels. Therefore, introducing αGIs into the diet may prevent diabetes.

In Asian countries, mulberry leaves are a known traditional medicine for preventing diabetes. According to a prior study, mulberry leaves have a potent αGI activity because of 1-deoxynojirimycin (DNJ), a glucose analog. In this chapter, we describe a method for determining DNJ in mulberry leaves; we also describe development of food-grade DNJ-enriched mulberry leaf extract (ME). Furthermore, we review the efficacy of this extract for postprandial glycemic control through human trials aimed at investigating use of mulberry leaves as food to prevent diabetes.

2. Development of ME

2.1 Diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels. Type 2 diabetes, defined as noninsulin-dependent diabetes mellitus (NIDDM), is the most common form that affects 90–95 percent of all adults who develop diabetes. Type 2 diabetes is a lifestyle disease caused by reduced insulin production or impaired insulin response in target organs. It is associated with genetic background, obesity, unhealthy dietary habits, and physical inactivity. Hyperglycemia-induced oxidative stress causes serious diabetic complications such as diabetic retinopathy, nephropathy, and neuropathy, leading to

decreased quality of life. The International Diabetes Federation (IDF) estimates that 285 million people around the world have diabetes; this total is expected to rise to 438 million within 20 years. Each year, a further 7 million people develop diabetes (IDF Diabetes Atlas fourth edition committee, 2009).

Type 2 diabetes increases morbidity and mortality as a result of serious macrovascular complications such as cardiovascular disease (Krolewski et al., 1987; Kannel & McGee, 1979). Recent epidemiological studies suggest that postprandial hyperglycemia is an independent risk factor for cardiovascular disease that has a greater effect on the development of this disease than fasting hyperglycemia (Ceriello, 1998; Hanefeld et al., 1996). Therefore, postprandial glycemic control is essential for effective reduction in the risk of cardiovascular disease. Carbohydrates comprise about 50% of our daily intake of calories. Carbohydrates ingested as food are digested to disaccharides by salivary and pancreatic amylases. The disaccharides are then hydrolyzed to monosaccharides by α-glucoside at the small intestine brush border and absorbed into the blood. α-Glucosidase is involved in this final step of carbohydrate digestion prior to absorption. αGIs retard the digestion and absorption of carbohydrates in the small intestinal lumen and therefore reduce the increase in blood glucose concentrations after a carbohydrate load. Acarbose, miglitol, and voglibose are α-glucosidase inhibitory agents used widely in clinical practice. These αGIs decrease both postprandial hyperglycemia and hyperinsulinemia but do not induce hypoglycemia and have a good safety profile, although their gastrointestinal adverse effects may limit long-term compliance to therapy. Long-term intervention trials of αGIs in patients with type 2 diabetes and IGT have been conducted. Recent placebo-controlled, prospective trials, including the STOP-NIDDM Trial and Victory Study, demonstrated that αGI intake before each meal reduces the risk of type 2 diabetes in patients with IGT (Chiasson et al., 2002, 2003; Kawamori et al., 2009). Therefore, improvement in postprandial hyperglycemia by αGI leads to prevention of diabetes and provides the basis for studies on the use of naturally occurring αGIs in plant foods.

2.2 Mulberry

Mulberry is a tree belonging to the genus *Morus* of the family Moraceae (Fig. 1). It is distributed over a wide area of tropical, subtropical, and temperate zones in Asia, Europe, North America, South America, and Africa. There are at least 24 species of mulberry with more than 100 known cultivars (Koidzumi, 1917). Historically, the trees have been planted for sericulture in east, central, and southern Asia. On the basis of folklore remedies, the leaves have also been used as a Chinese herbal tea, especially for diabetes. In the modern era, health benefits from mulberry products have been verified scientifically, with mulberry shown to have potent α-glucosidase inhibitory activity mainly because of azasugars. This has led to proposals that dietary mulberry intake is beneficial for attenuating postprandial hyperglycemia, thereby preventing diabetes. Several animal studies have been conducted to date. Nojima and co-workers showed that administration of mulberry leaf extract restored impaired glucose metabolism and hyperglycemic conditions in streptozotocin-induced diabetic mice (Nojima et al., 1998; Kimura et al., 1995). At present, various mulberry food products, including teas, powders, and tablets, are commercially available in Japan and many other countries. Although these products have apparent antidiabetic effects, their efficacy in humans requires further study.

Fig. 1. Mulberry (*Morus alba* L.)

2.3 Azasugars in mulberry

Azasugars are alkaloids that mimic the structures of monosaccharides. In azasugars, the oxygen atom in the ring of these sugars is replaced by nitrogen. The first azasugar, the antibiotic nojirimycin, was discovered in 1966 in *Streptomyces* microorganisms (Inoue et al., 1966). Since then, more than 100 azasugars have been isolated from plants and microorganisms. DNJ is a 5-amino-1,5-dideoxy-D-glucopyranose or D-glucose analog (Fig. 2). Initially, DNJ was chemically synthesized by reduction of nojirimycin (Inoue et al., 1967) ; later, naturally occurring DNJ was isolated from the roots of mulberry trees and called moranoline (Yagi et al., 1976). DNJ has also been produced by microorganisms such as *Bacillus* and *Streptomyces* (Schmidt et al., 1979; Murao & Miyata, 1980; Ezure et al., 1985). Mulberry leaves are relatively rich in azasugars such as DNJ, fagomine, N-methyl-DNJ, and 2-O-R-D-galactopyranosyl-DNJ. DNJ is the dominant alkaloid, accounting for 50% of mulberry azasugars (Asano et al., 2001).
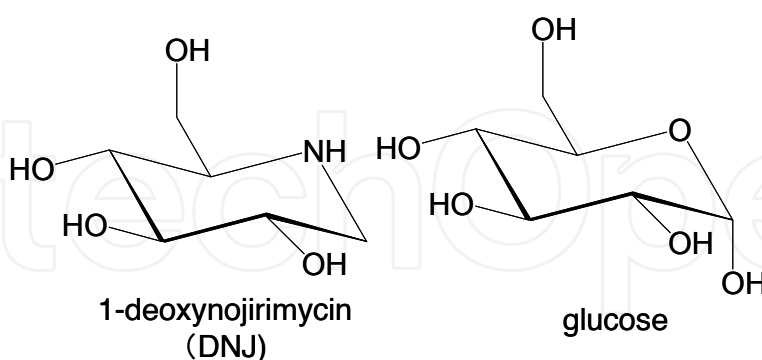

Fig. 2. Chemical structure of DNJ and glucose

Azasugars have α-glucosidase inhibitory properties because of their ability to competitively bind to the active sites of glucosidases by mimicking the corresponding natural substrates (Fig. 3). The αGI clinical agents described above are all azasugars developed from natural occurring azasugars (Junge et al., 1996). Among the naturally occurring azasugars, DNJ shows potent α-glucosidase inhibitory activity. Consequently, miglitol was developed as a lead compound from DNJ.

Based on this background, the relationship between the concentration of DNJ and the antidiabetic effect of mulberry food has attracted considerable attention. For this reason, mulberry food containing DNJ needs to be prepared.
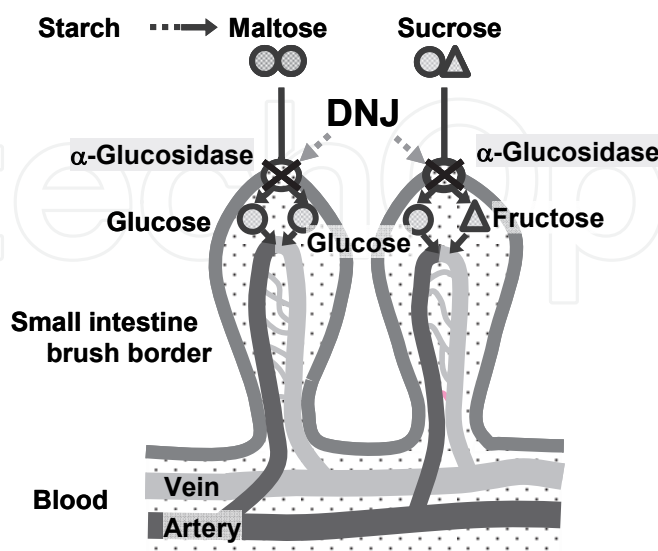

Fig. 3. Possible mechanism of DNJ in the digestive tract

2.4 Methods for determining DNJ in mulberry

Determination of DNJ levels in mulberry has been difficult because of the high polarity of DNJ and the absence of a chromophore in the molecule. Therefore, DNJ is too hydrophilic to be retained by widely used reverse-phase chromatography columns, and it cannot be detected with common ultraviolet or fluorescence detectors. Ligand-exchange and aminopropyl columns are commonly used for HPLC determination of relatively polar compounds such as carbohydrates and water-soluble vitamins (Sharpless et al., 2000). However, even these columns do not achieve reasonable retention of DNJ, and for this reason, several other methods have been developed for determining DNJ in mulberry.

Kimura et al. reported a method that used hydrophilic interaction liquid chromatography (HILIC) coupled with an evaporative light-scattering detector (ELSD) (Kimura et al., 2004); This method is known as the HILIC-ELSD method. HILIC has been developed as an efficient tool for analyzing highly hydrophilic compounds, and its analytical application to carbohydrates (Alpert et al., 1994) and peptides (Alpert et al., 1990) has been reported. The retention ability of the HILIC column basically depends on the hydrophilicity of the analytes, and if the compound has amino groups, its retention time is increased (Tolstikov & Fiehn, 2002). Therefore, a HILIC column is preferable for efficient separation of azasugars. ELSD is the universal detector that responds to nonvolatile compounds and directly detects analytes lacking chromophores.

Kim et al. (2003) reported the procedures for deriving DNJ using 9-fluorenylmethoxycarbonyl chloride, which targets secondary amino groups in DNJ, followed by reverse-phase HPLC using a fluorescence detector.

Furthermore, several other methods, such as HILIC-MS/MS (Nakagawa et al., 2010) and anion-exchange chromatography with pulsed amperometric detection methods (Yoshihashi et al., 2010), have been developed for measuring DNJ levels.

2.5 Development of ME

Since the putative effective dose of more than 10 mg DNJ per individual weighing 60 kg cannot be generally provided by commercially available mulberry leaf products because of their low DNJ content, the development of DNJ-enriched products is highly desired. Therefore, to produce nutraceutical ME, the concentrations of DNJ in mulberry leaves from different cultivars, harvest seasons, and leaf locations were examined. DNJ concentrations differed according to cultivars, with *M. alba* L. var. Tsuruta and Hayatesakari having a high DNJ content. The harvest season and region of mulberry leaves were also closely related to the DNJ content, with young mulberry leaves from the top part of the branches in the summer having the highest DNJ concentration. After optimization of harvesting and processing, ME was produced containing 1.5 % DNJ. This powder contained DNJ at concentrations approximately 15 times higher than general mulberry products (Figs. 4, 5; Kimura et al., 2007).

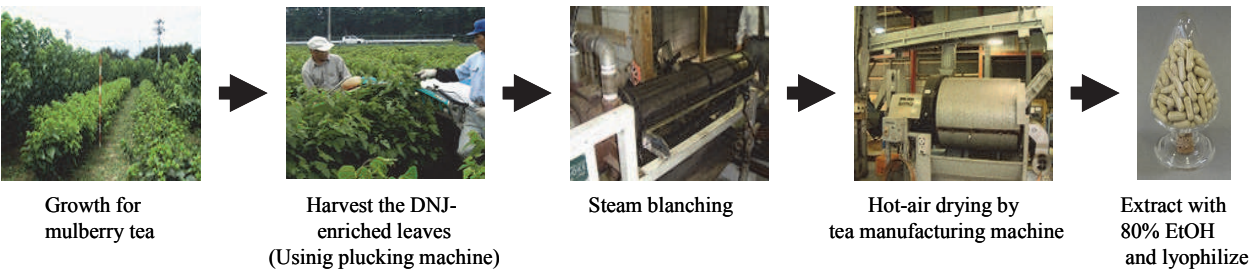| Growth for mulberry tea | Harvest the DNJ-enriched leaves (Usinig plucking machine) | Steam blanching | Hot-air drying by tea manufacturing machine | Extract with 80% EtOH and lyophilize |

Fig. 4. Improved production process for DNJ-enriched mulberry extract (ME) (modified from Ref. Kimura, 2010; used with permission)

Young mulberry leaves from the top part of the branches in August contained the highest amount of DNJ. For harvesting, a method involving a plucking machine was considered an effective way for collecting young leaves. For blanching, steam treatment was used to prevent leaching of DNJ. For the drying process, hot air was employed, and the dried leaves were then disintegrated and added to a mixture of ethanol and water (20:80, v:v). After filtration, the extract was concentrated and lyophilized to a powder.
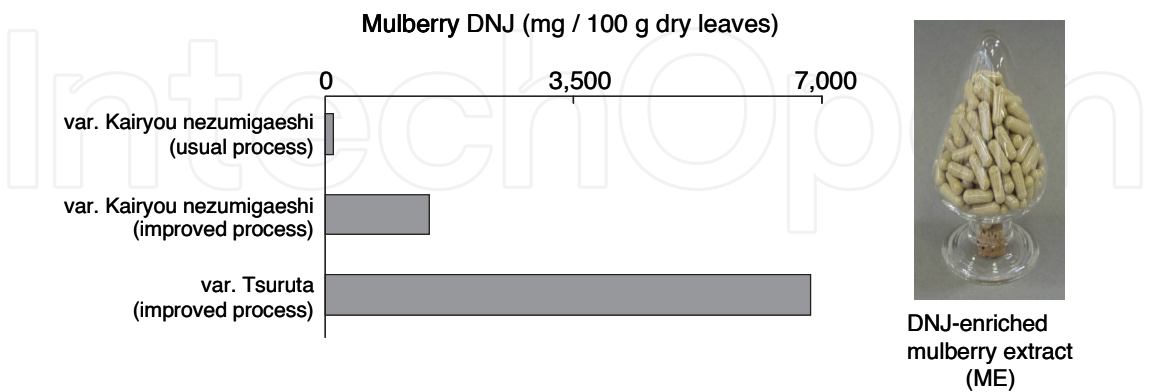

Fig. 5. DNJ concentrations in mulberry products produced by different processes (modified from Ref. Kimura, 2010; used with permission)

In the traditional process, widely cultivated leaves (*M. alba* L. var. Kairyou nezumigaeshi) were collected from whole branches and dried using hot air. In the improved process, the

DNJ content in the extract (*M. alba* L. var. Kairyou nezumigaeshi) was 15 times higher than that in the traditional mulberry product. If mulberry leaves containing high levels of DNJ (e.g., *M. alba* L. var. Tsuruta) were used, products with considerably greater DNJ concentrations could be produced.

3. Evaluation of ME

3.1 *In vitro* α-glucosidase inhibitory activity

The rat intestinal α-glucosidase inhibitory activity of ME was measured with *p*-nitrophenyl-α-D-glucopyranoside as the substrate (Yamaki & Mori, 2006). ME showed potent α-glucosidase inhibitory activity, which was approximately the same as the activity of the DNJ content in ME. This implied that the α-glucosidase inhibitory activity of ME was attributable to DNJ.

3.2 Single oral administration test

ME showed potent *in vitro* α-glucosidase inhibitory activity. Human intervention trials with ME were conducted. To clarify the effect of improving postprandial hyperglycemia and the efficacious dose of ME, single oral administration tests were performed.

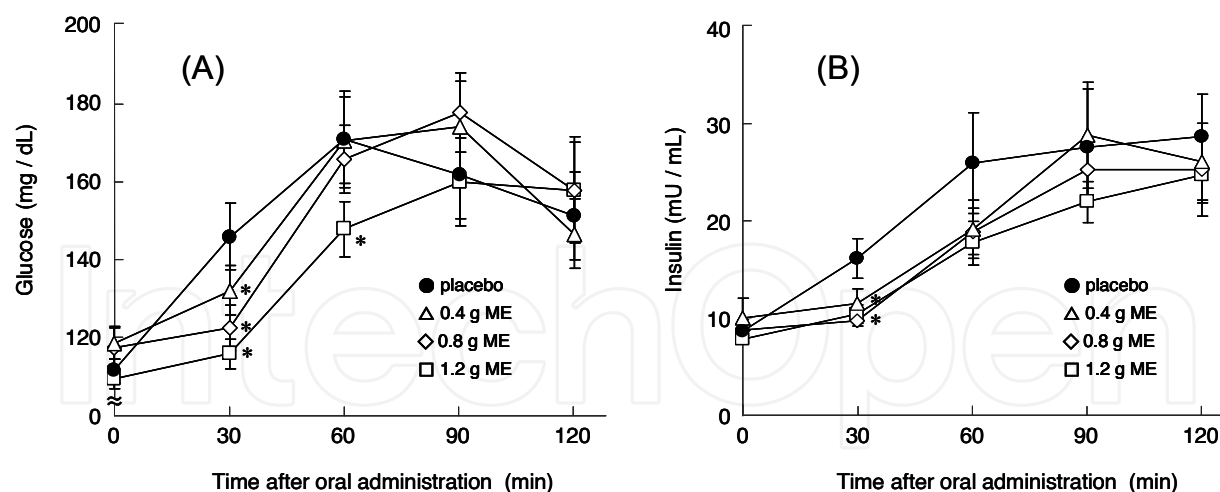### 3.2.1 Sucrose tolerance test in healthy subjects

Twenty-four healthy volunteers were randomly divided into four groups of six individuals. After fasting overnight, the individuals in each group received either 0 (placebo), 0.4, 0.8, or 1.2 g ME (corresponding to 0, 6, 12, or 18 mg DNJ, respectively), followed by 50 g sucrose dissolved in 100 mL water. Blood samples were collected before and 30, 60, 90, 120, 150, and 180 min after DNJ or sucrose administration. Plasma glucose and insulin levels were then measured. The results showed that oral administration of 0.8 and 1.2 g ME significantly suppressed the elevation of postprandial blood glucose and secretion of insulin (Kimura et al., 2007).

3.2.2 Carbohydrate tolerance test in subjects with borderline diabetes

To examine the diabetes preventative effect of ME in a practical daily meal, a carbohydrate tolerance test was performed in subjects with borderline diabetes. The study design was a randomized, double-blind, four-period, crossover trial. Twelve volunteers with impaired glucose metabolism [fasting plasma glucose (FPG) in the range of 100–140 mg/dL] were enrolled in the study. In each trial, all the subjects consumed 200 g boiled white rice 15 min after ME ingestion. Blood samples were drawn before ME ingestion and 30, 60, 90, and 120 min after starting the meal. Plasma glucose, plasma insulin, and other biochemical parameters were then measured. Similar to the study described above, administration of 0.8 and 1.2 g ME caused significant suppression and peak time delay of postprandial blood glucose and secretion of insulin (Fig. 6; Asai et al., 2011).

3.3 Long-term supplementation trial

Elevation of postprandial blood glucose levels and secretion of insulin were suppressed significantly at a dose of more than 0.8 g ME. To assess the safety and effects of long-term ingestion, a long-term supplementation trial was then conducted.

After fasting for 12 h, the subjects with borderline diabetes were orally administered either 0 (placebo), 0.4, 0.8, or 1.2 g ME (0, 6, 12, or 18 mg DNJ, respectively), followed by 200 g boiled rice. Blood samples were collected prior to intake and 30, 60, 90, and 120 min after rice intake. The plasma glucose and insulin levels were then determined. Data represent the mean ± S.E.M. (n = 10). *P < 0.05 vs. placebo.

Fig. 6. Effects of a single oral administration of ME on plasma glucose (A) and insulin (B) levels (from Ref. Asai et al., 2011; used with permission)
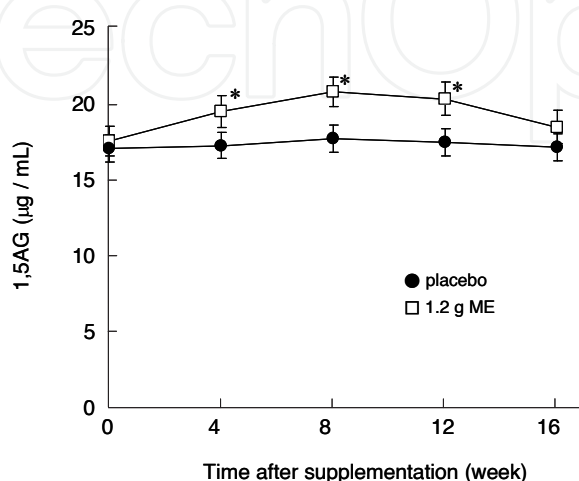
3.3.1 Thirty-eight–day supplementation trial in healthy subjects

Twelve healthy volunteers were enrolled in the study. Based on the results of the above described single oral administration test, the ME dose was set at 1.2 g before every meal. The subjects were randomly divided into two groups; they received either 0 (placebo) or 1.2 g ME before every meal for 38 days (0 or 3.6 g/day, corresponding to 0 and 54 mg DNJ/day, respectively). Fasting blood samples were collected on days 0, 24, and 38 of ME powder administration. Blood biochemical parameters such as FPG, insulin, glycated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (Tcho), HDL cholesterol (HDL-C), adiponectin, high-molecular-weight adiponectin (HMW adiponectin), and lipoprotein lipase (LPL) were measured. The results showed no significant differences in any of the biochemical parameters between the placebo group and the group ingesting the test food either before, during, or after the study. The daily intake of the ME powder did not cause hypoglycemia or abnormal lipid profiles (i.e., high cholesterol). According to previous reports, long-term ingestion of αGI (acarbose, tochi extract) reduced FAG, HbA1C, TG, and Tcho levels in the subjects (Fujita et al., 2003; Hillerbrand et al., 1979), changes which may contribute to diabetes prevention and improvement. The results of our study showed no such effects, which could be attributable to the short administration period. The major side effects of αGI involve the gastrointestinal system (Harano et al., 2002). However, no subjects in our study complained of negative gastrointestinal system-related side effects such as abdominal distension, abdominal pain, retching, or flatulence (Kimura et al., 2008).

3.3.2 Twelve-week supplementation trial in subjects with borderline diabetes

Next, we conducted a 12-week randomized, double-blind, placebo-controlled trial, followed by a 4-week posttreatment observation in subjects with borderline diabetes. Seventy-six subjects with FPG in the range of 110–140 mg/dL were recruited and randomized to receive either mulberry leaf extract or placebo. During the 12-week trial, ME (18 mg DNJ) or

identical placebo capsules were taken three times a day before meals. Anthropometric data and blood samples were collected from the subjects after they had fasted overnight every 4 weeks of the supplementation period (week 0, 4, 8, and 12) and 4 weeks after withdrawal of the supplementation (week 16). Adverse effects were assessed by interview and self-reports. Blood biochemical parameters such as FPG, insulin, HbA1c, glycated albumin (GA), 1,5-anhydroglucitol (1,5AG), TG, Tcho, HDL-C, adiponectin, HMW adiponectin, and LPL were measured.

Changes in the concentration of 1,5AG during the 12-week supplementation with either ME (18 mg DNJ, thrice daily) or placebo followed by a 4-week observation without supplementation Data are expressed as the mean ± S.E.M. (n = 33 in the extract group, n = 32 in the placebo group). *P < 0.05 vs. placebo.

Fig. 7. Effects of 12-week supplementation of ME on plasma 1,5AG levels (modified from Ref. Asai et al., 2011; used with permission)

The results showed that there were no significant differences between the ME and placebo groups in baseline values or values during the study for the glycemic control parameters (FPG, insulin, HbA1c, GA), anthropometric measurements, or serum lipid profiles. Among the glycemic control parameters, there were significant differences between the two groups with regard to the change in serum 1,5AG concentration over the study period. The 1,5AG concentration of the ME group increased gradually from baseline through to weeks 4, 8, and 12 and was higher than that in the placebo group at weeks 4, 8 and 12. The increase in 1,5AG concentration in the ME group returned to the baseline level after the 4-week posttreatment observation period (i.e., at week 16) (Fig. 7). The serum 1,5AG concentration is maintained at a constant level under euglycemic conditions; however, it decreases as a result of competitive inhibition of renal tubular reabsorption caused by glycosuria under hyperglycemic conditions (Akanuma et al., 1988; Yamanouchi et al., 1990). Serum 1,5AG concentrations therefore sensitively respond to blood glucose fluctuations within a few days (Yamanouchi et al., 1992, 1996; Dungan et al., 206). Hence, the increased 1,5AG concentration we observed may reflect a continuous reduction in postprandial hyperglycemic spikes over the 12-week supplementation period. The increase in the 1,5AG concentration returned to baseline levels after the 4-week withdrawal of ME supplementation. On the other hand, no significant differences in FPG, HbA1c, or GA concentrations were observed between the groups. While the 1,5AG concentration

responded to glycemic fluctuations within a few days, the HbA1c and GA concentrations reflected time-averaged glycemia in the previous 2–3 months and 2–3 weeks, respectively. In contrast to this result, meta-analysis of αGI drug trials in patients with type 2 diabetes showed that FPG and HbA1c concentrations were reduced by acarbose and miglitol (Van Der Laar et al., 2005). Because the subjects in these trials had diabetes, their baseline HbA1c and FPG concentrations were considerably higher than those of subjects in the present trial. Moreover, these earlier trials were conducted for considerably longer durations.

Gastrointestinal symptoms such as abdominal distension, diarrhea, and flatulence are the most frequent adverse effects of αGI agents. No such adverse effects were observed through the study period (Asai et al., 2011).

4. Conclusion

Increasing evidence strongly supports the efficiency of interventions such as diet and exercise for preventing or delaying the onset of diabetes in prediabetic individuals. Pharmacological approaches are another effective strategy for achieving these objectives.

Mulberry leaves have been used in folk medicine for treating diabetes since ancient times. Three decades ago, DNJ, a potent αGI, was found in mulberry leaves. Since this discovery, DNJ has been considered to be responsible for the antidiabetic effect of mulberry leaves. However, there is only limited information on the efficacy and effective dose of DNJ in humans. Recently, food-grade mulberry leaf extract with a defined DNJ concentration (1.5%) has been developed. Human studies involving ingestion of the extract prior to meals showed suppression of postprandial hyperglycemia and hyperinsulinemia. In addition, studies on long-term supplementation of the extract at reasonable doses showed an improvement in postprandial glycemic control. Hypoglycemia; abnormal lipid profiles; gastrointestinal system-related side effects such as abdominal distension, abdominal pain, retching, or flatulence; or any other adverse effects have also not been observed. Therefore, DNJ in mulberry leaves appears to be a promising therapy for preventing or delaying the onset of diabetes, especially in prediabetic or mildly diabetic individuals.

As described above, we have gathered favorable evidence for the efficacy of ME. However, in terms of safety, there is insufficient evidence because of a lack of history of mulberry as a food for humans. Further safety evaluation on the absorption, distribution, metabolism, and excretion of mulberry DNJ is therefore required before the plant can be deployed as a functional food.
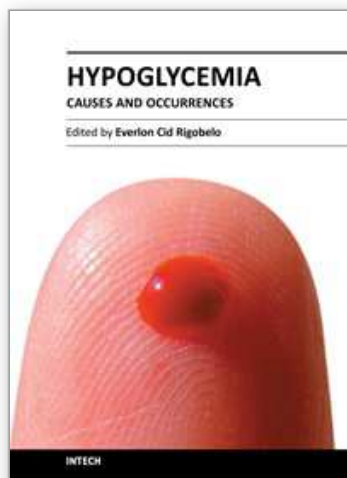
5. Acknowledgements

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Hypoglycemia - Causes and Occurrences

Edited by Prof. Everlon Rigobelo

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