

# Influence of Mulberry Leaf Extract on the Blood Glucose and Breath Hydrogen Response to Ingestion of 75 g Sucrose by Type 2 Diabetic and Control Subjects

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In Asia, type 2 diabetes is treated with mulberry leaf. Studies supporting this usage include the demonstration that mulberry leaf (1) reduced blood glucose in normal rats (1) and rats with diabetes induced by streptozotocin (2) or alloxan (3), (2) reduced fasting blood glucose and A1C concentrations in 12 subjects with type 2 diabetes (4), and (3) relative to glybenclamide therapy, reduced fasting blood glucose, serum lipids, and lipid peroxidation indicators in subjects with type 2 diabetes (5). In the present study, we determined whether co-ingestion of mulberry extract with 75 g sucrose influenced the blood glucose response and sucrose absorption of type 2 diabetic and control subjects.

## RESEARCH DESIGN AND METHODS

Participants included 10 healthy control subjects (aged 24–61 years) and 10 type 2 diabetic subjects without complications who were receiving oral hypoglycemic agents (aged 59–75 years; glycohemoglobin  $7.1 \pm 0.9\%$  [normal  $<6.2\%$ ]). The study was approved by the Minneapolis VA Medical Center Human Studies Committee. Mulberry leaf extract was provided by NatureGen (San Diego, CA). Placebo (red dye #40 and caramel) was similar in color and taste to the mulberry.

At 8 A.M., subjects randomly ingested mulberry extract (1 g) or placebo plus 75 g sucrose in 500 ml hot water. The test

was repeated in 1 week with the opposite treatment. Medications (except acarbose) were allowed. Hourly breath samples for H<sub>2</sub> measurements (6) were obtained for 8 h. Blood glucose was assessed via finger stick (AccuCheck; Roche Diagnostics, Indianapolis, IN) before and at intervals over 120 min after sucrose ingestion in control subjects and additionally at 180 and 240 min in type 2 diabetic subjects. A low H<sub>2</sub>-producing lunch was provided after completion of glucose measurements. On the test day, subjects kept a diary of severity of abdominal and other symptoms rated on a linear scale (0 = none through 4 = severe) (7).

**Calculations and statistics.** Because blood glucose concentrations often declined below baseline after 120 min, the significance of differences of blood glucose increases between extract and placebo was determined by ANOVA of values obtained over the initial 120 min. The statistical model included treatment and time as repeated measures and the interactions of treatment and time. The influence of treatment on breath H<sub>2</sub> was determined from differences between areas under the curves for 8 h (two-tailed paired *t* test). Sucrose malabsorption was estimated from breath H<sub>2</sub> concentrations (8).

**RESULTS**— Compared with placebo, co-ingestion of mulberry produced significant reductions in blood glucose in-

creases for the initial 120 min of the study (Fig. 1). The mean  $\pm$  SD increases in glucose for mulberry versus placebo over this period were  $15 \pm 18$  vs.  $22 \pm 33$  mg/dl ( $P = 0.005$ ) for control subjects and  $42 \pm 28$  vs.  $54 \pm 46$  mg/dl ( $P = 0.002$ ) for type 2 diabetic subjects. Placebo was associated with greater glucose declines below fasting at the tail end of the study (Fig. 1). The peak-to-trough difference in blood glucose concentration was significantly ( $P < 0.001$ ) less for mulberry versus placebo for both groups.

Breath H<sub>2</sub> concentration was greater ( $P < 0.01$ ) in the mulberry versus the placebo treatment for both subject groups. Sucrose malabsorption with the extract was estimated to be 12 and 16 g for the control and diabetic subjects, respectively. There was no significant difference in severity for any symptom between mulberry- and placebo-treated subjects; 3 of 20 subjects receiving mulberry or placebo reported mild gas and/or bloating.

**CONCLUSIONS**— The co-ingestion of mulberry extract with 75 g sucrose significantly reduced the increase in blood glucose observed over the initial 120 min of testing in control and type 2 diabetic subjects (Fig. 1). Blood glucose declines at the tail end of the study were less with extract. Thus, peak-to-trough fluctuations in blood glucose were markedly reduced by mulberry ingestion.

The mulberry-induced reduction in blood glucose presumably reflects the ability of mulberry to inhibit intestinal sucrose (9). The increased H<sub>2</sub> observed with mulberry indicates that this supplement induced sucrose malabsorption.

The reduction of blood glucose at early time points but higher values at later time points with mulberry would yield relatively minor alterations in A1C. However, factors other than A1C concentrations may play a role in the microvascular complications of diabetes (10,11). Brownlee (12) proposed that generation of reactive oxygen species is the common pathway responsible for diabetes complications, and glucose fluctuations are associated with

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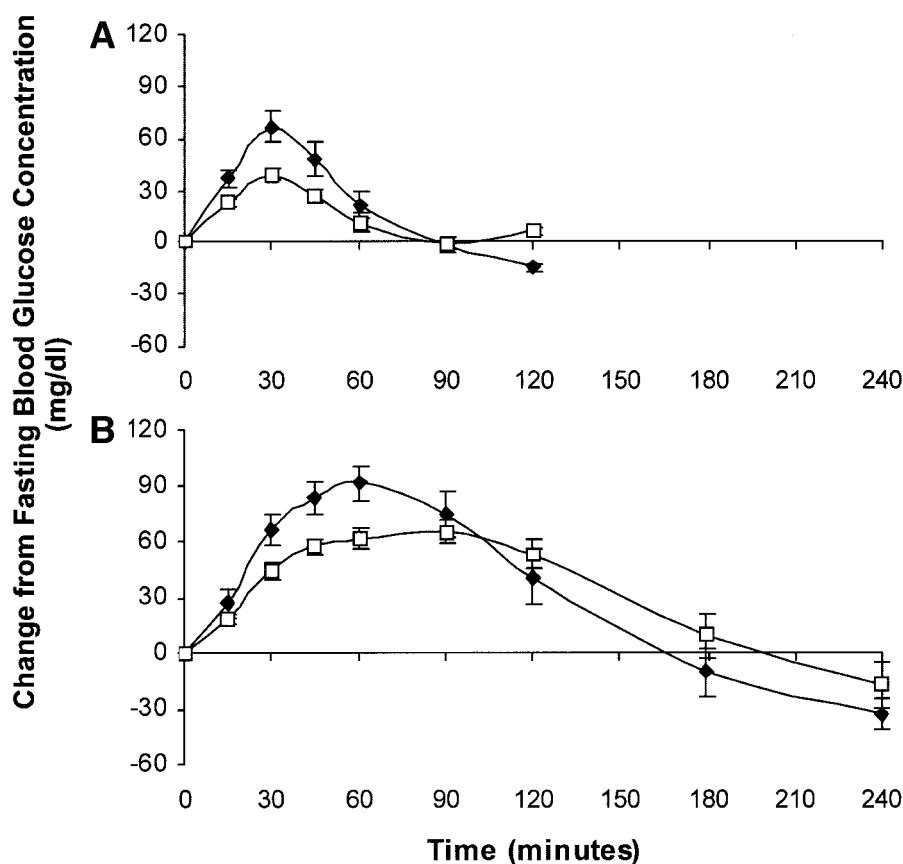
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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Figure 1**—Changes in blood glucose concentration from the fasting concentration of 10 healthy control subjects (A) and 10 type 2 diabetic subjects (B) after ingestion of 75 g sucrose with 1.0 g mulberry leaf extract (□) or placebo (◆). The difference between mulberry and placebo over the first 120 min of the study, determined by ANOVA, was highly significant for control ( $P = 0.005$ ) and diabetic ( $P = 0.002$ ) subjects.

increased markers of oxidative injury (13). Thus, reductions in blood glucose fluctuation with mulberry extract might reduce diabetes complications despite minor reduction of A1C.

Two drugs (acarbose and miglitol) that inhibit carbohydrate digestion produce modest reductions in fasting blood glucose and A1C (14) and slow progression of glucose intolerance to overt diabetes (15). Use of these drugs has been limited by associated bloating, gas, and diarrhea (16). These symptoms were not significantly increased by mulberry extract; however, convincing evidence of lesser side effects will require studies with extract ingested with each major meal.

Some individuals prefer an herbal over a pharmaceutical preparation, and such individuals might find mulberry extract more acceptable and better tolerated than acarbose or miglitol. In addition, mulberry extract contains compounds such as fagomine, which induces insulin se-

cretion (17), and antioxidants that putatively reduce lipid peroxidation (5,18,19).

While mulberry leaf is considered safe as a drug and a foodstuff in Asia (20), the extract contains multiple constituents, increasing the potential for idiosyncratic reactions. While unlikely, such reactions can be excluded only after extensive, monitored use of the extract.

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