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EFFECT OF *STEVIA REBAUDIANA* ON GLUCOSE TOLERANCE IN NORMAL ADULT HUMANS

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The effect of aqueous extracts of *Stevia rebaudiana* leaves on a glucose tolerance test was investigated in 16 normal volunteers. Aqueous extracts of 5 grams of leaves were administered to volunteers at regular 6-h intervals for 3 days. Glucose tolerance tests were performed before and after extract administration. A second group of 6 normal volunterrs who ingested an aqueous arabinose solution was also studied to eliminate possible stress effects. The extract of *Stevia rebaudiana* increased glucose tolerance. The extract significantly decreased plasma glucose levels during the test and after overnight fasting in all volunteers.

Key words: *Stevia rebaudiana*, glucose tolerance.

Stevia rebaudiana is a shrub indigenous to Brazil and Paraguay belonging to the Compositae family (1). Five percent of the dry weight of the leaves of this plant is stevioside, a carbohydrate which is 300 times sweeter than sucrose (1). In recent years it has become important as a non-caloric sweetener in Japan and Brazil. In addition to stevioside, the leaves of *Stevia rebaudiana* also contain several structurally related compounds such as rebaudioside A (2% dry weight), rebaudioside B, steviolbioside, and steviol (2), several of which are sweet.

Many studies have demonstrated physiologic and therapeutic effects of Stevia. It has been claimed that this plant has cardiotonic (3), contraceptive (4) and hypoglycemic properties. The latter of these properties was first described by Miquel (5) in studies of diabetic patients and similar effects have been observed in alloxan-diabetic rabbits (6). In contrast, Suzuki *et al.* (7) have shown that liver glycogen content as well as plasma glucose levels are decreased in rats fed a diet containing a 10% supplement of powdered Stevia leaves.

We now report a systemic study of hypoglycemic effects of *Stevia rebaudiana* in normal volunteers. Glucose tolerance tests (GTT) were performed in adult subjects before and after ingestion of aqueous extracts of Stevia leaves (20 g/day) during a 3-day period.

Stevia rebaudiana leaves were obtained from the experimental farm of Maringá University. The aqueous extracts from the leaves was prepared by immersing them in boiling water for 20 min. Twenty-two healthy adult volunteers both male and female, who were not using any medication and who showed no symptoms of sickness, participated in the study. Sixteen volunteers were subjected to the first glucose tolerance test. Afterwards, extracts corresponding to 5 g of extracted leaves were administered orally to volunteers at 6-h intervals. The first dose was administered 21 h after the initial GTT and 2 h before the second GTT. Each patient received the extract of 65 g of dry leaves in 13 doses. A control group of 6 people received 13 doses of 250 mg arabinose on the same schedule to evaluate the possible schedule effect on the glucose tolerance response.

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Arabinose was used because of its high content in the Stevia extract. During the experimental period the volunteers ate normal diets. They did not have anorexia and their body weight remained unchanged. The glucose tolerance test was performed according to the recommendations of the Committee on Statistics of the American Diabetes Association. One hundred grams of glucose was orally administered after overnight fasting. Two milliliters of blood was withdrawn from the radial vein for blood glucose determination by the o-toluidine method (8) before ingestion and 30, 60, 90, 120 and 180 min afterwards. Glycosuria was detected with glucotest tapes.

The plasma glucose levels measured after Stevia treatment were significantly lower than the control at each time tested (Figure 1). The maximal difference coincided with the highest glucose level detected during the GTT, which was at 30 min.

Only one volunteer exceeded the renal threshold for glycosuria measured during the first 90 min. After Stevia treatment his glycosuria was completely abolished.

Figure 2 shows the results obtained for individuals who received 250 mg of arabinose rather than Stevia extract. There was no difference between the first GTT (control) and the GTT measured after arabinose administration ($P > 0.05$).

The results obtained in the present study of normal volunteers agree with those obtained in diabetic patients (5) and alloxanized rabbits (6). In every period studied the glycemia was diminished after Stevia treatment, including overnight fasting (basal).

Several studies have been performed to

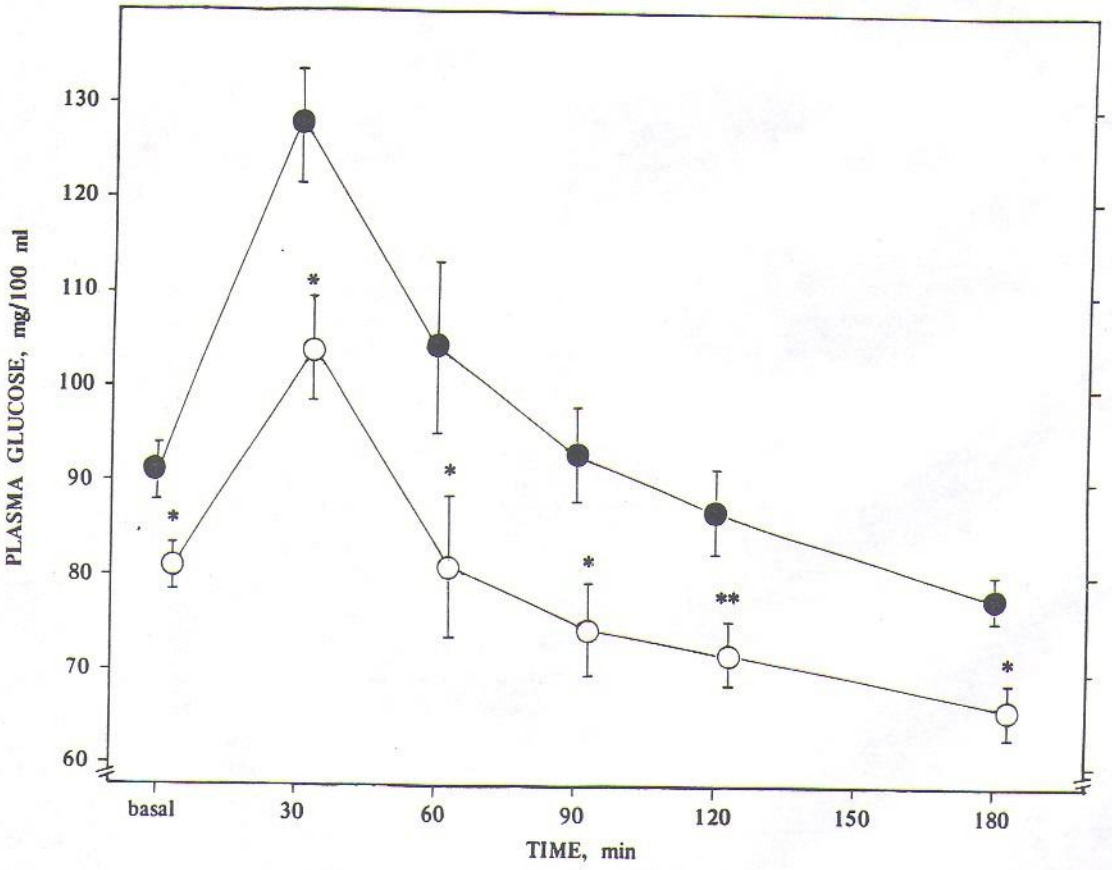

Figure 1 - Effect of the leaf extract of *Stevia rebaudiana* on blood glucose tolerance. Data are reported as mean ± SEM for 16 volunteers. ●, Control; ○, after Stevia treatment; * $P < 0.01$; ** $P < 0.05$.

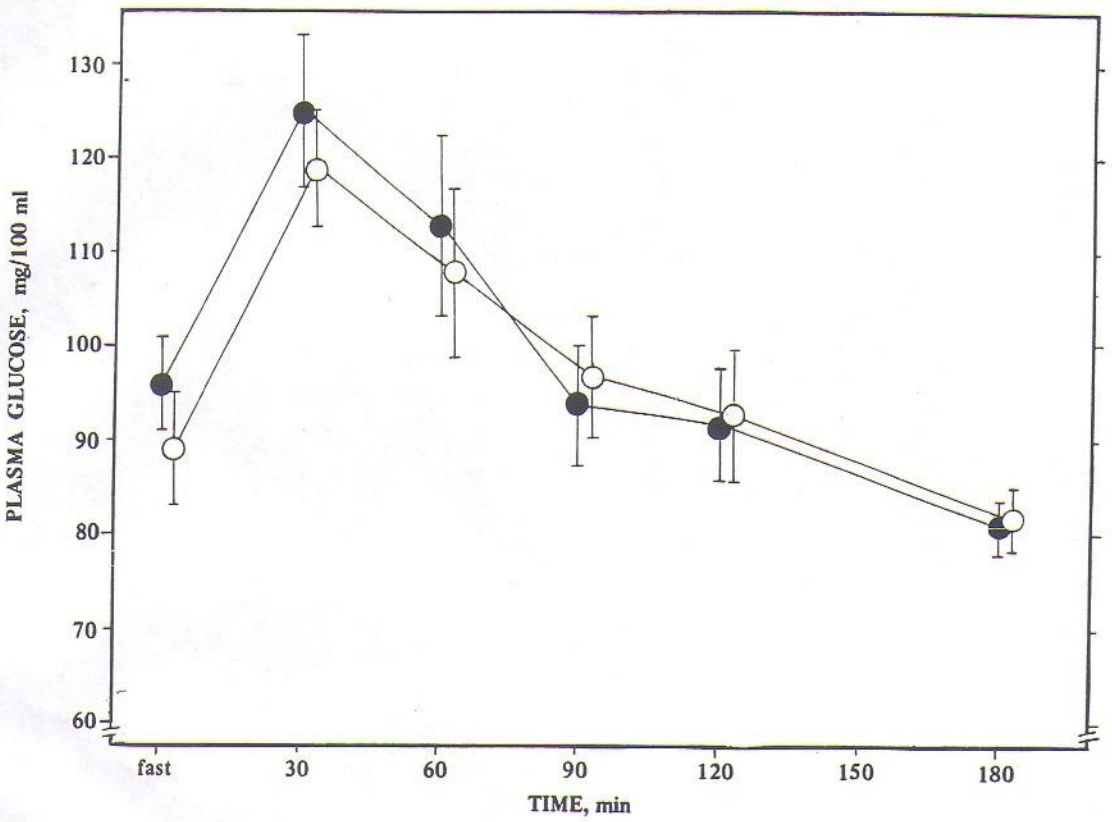

Figure 2 - Effect of arabinose ingestion (1 g/day) on the glucose tolerance test. Data are reported as mean ± SEM for 6 volunteers. ●, Control; ○, after arabinose treatment.

determine the mechanisms involved in the physiological effects of Stevia aqueous extracts. Stevioside, isosteviol, steviolbioside and steviol, derivatives of the plant leaves, inhibit oxidative phosphorylation in isolated rat liver mitochondria via mechanisms which include inhibition of nucleotide exchange (9), uncoupling of respiration (10), inhibition of NADH-oxidase, L-glutamate dehydrogenase and succinate dehydrogenase (11, 12). These effects can provoke an increase in glucose utilization and lactate production (13). In this respect, they behave like actractyligenin, a potent inhibitor of adenine nucleotide exchange and of oxidative phosphorylation in mitochondria (9, 14). It has also been shown that there is a potent inhibitory effect of Stevia derivatives on gluconeogenesis of renal tubules and liver (15). In fact, in intact cells, atractyloside inhibits gluconeogenesis and respiration (16), as has been reported for steviol and its analogues (13). It is generally accepted that the inhibition of gluconeogenesis is able to lead to hypoglycemia. Thus, some substances which inhibit gluconeogenesis are therapeutic to diabetes. This is the case of phenphormin (17), 3-mercapto picolinate (18) and atractyloside (14). In some experiments it has been shown that these drugs can provoke hypoglycemic convulsions (14).

It is possible that the Stevia extract, by increasing the mitochondrial respiration rate and inhibiting the gluconeogenetic pathway, can indeed lead to hypoglycemia. Nevertheless, a possible effect of this plant on insulin secretion or peripheral action should be considered.

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