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Hypoglycemic effect of the water extract of *Smallantus sonchifolius* (yacon) leaves in normal and diabetic rats

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Abstract

The hypoglycemic effect of the water extract of the leaves of *Smallantus sonchifolius* (yacon) was examined in normal, transiently hyperglycemic and streptozotocin (STZ)-induced diabetic rats. Ten-percent yacon decoction produced a significant decrease in plasma glucose levels in normal rats when administered by intraperitoneal injection or gastric tube. In a glucose tolerance test, a single administration of 10% yacon decoction lowered the plasma glucose levels in normal rats. In contrast, a single oral or intraperitoneal administration of yacon decoction produced no effect on the plasma glucose levels of STZ-induced diabetic rats. However, the administration of 2% yacon tea ad libitum instead of water for 30 days produced a significant hypoglycemic effect on STZ-induced diabetic rats. After 30 days of tea administration, diabetic rats showed improved body (plasma glucose, plasma insulin levels, body weight) and renal parameters (kidney weight, kidney to body weight ratio, creatinine clearance, urinary albumin excretion) in comparison with the diabetic controls. Our results suggest that yacon water extract produces an increase in plasma insulin concentration. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: *Smallantus sonchifolius*; Plasma insulin; Plasma glucose; Creatinine

1. Introduction

In Argentina, plants have long been used for the empirical treatment of diabetes. In fact, world ethnobotanical information about medicinal plants reports almost 800 plants used in the control of diabetes mellitus, although only a few of them have been scientifically studied. *Smallantus sonchifolius* (= *Polymnia sonchifolia*, *Asteraceae*) or yacon is a perennial herb 1.5–3 m tall with a root system composed of 4–20 edible fleshy tuberous storage roots. The aerial stems, densely

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pubescent green to purplish, are cylindrical or subangular and hollow at maturity, with only a few branches in most clones. The lower leaves are broadly ovate and hastate or subhastate, connate and auriculate at the base, while the upper ones are ovate-lanceolate (for review see Grau and Rea, 1997). Yacon, considered by the early Andean inhabitants as a 'fruit', has a relatively low energy value despite its juiciness and sweet taste. At present, yacon is grown in many localities scattered throughout the Andes, from Colombia to northwestern Argentina. In Bolivia, yacon roots are commonly consumed by people suffering from diabetes or from various digestive or renal disorders. Certain medicinal properties have been attributed to yacon leaves in Brazil, where dried leaves are used to prepare an antidiabetic tea, although little scientific research has been carried out on the subject. Recently Volpato et al. (1997) obtained data suggesting that yacon leaves can reduce blood glucose levels.

The present investigation was undertaken to study the anti-hyperglycemic effect of yacon leaves in normoglycemic, transiently hyperglycemic and streptozotocin (STZ)-induced diabetic rats. The effect on several renal parameters of a 30 day administration of yacon tea in diabetic rats was also evaluated.

2. Materials and methods

2.1. Plant materials

Plant materials used in this study consisted of the leaves of *S. sonchifolius* (Poepp. and Endl) H. Robinson (Clone LIEY97-1), yacon, collected from Horco Molle, Province of Tucumán. Voucher specimens were deposited in the herbarium of Instituto 'Miguel Lillo', San Miguel de Tucumán, Tucumán, Argentina (No. 600982LIL). The dried leaves (20 g) were steeped in boiling water (200 ml) for 20 min and then allowed to cool at room temperature. Then the decoction was passed through a nitrocellulose filter (0.2 μm) and administered to the experimental animals. Tea infusion was prepared by pouring 1000 ml of boiling water onto 20 g of dried yacon leaves and stems. The extraction continued for 20 min while cooling. Extracts yield after freeze-drying was 1.8 and 2.2 g for decoction and tea infusion, respectively. Similar water extracts are the common form of administration used in popular medicine.

2.2. Animals

The experimental animals were male Sprague–Dawley rats (weight 230–260 g) raised in the animal facility of the Instituto de Biología, Universidad Nacional de Tucumán, Tucumán, Argentina. They were fed with a standard laboratory diet, given tap water ad libitum and kept under controlled temperature (23 ± 1°C), humidity (approximately 70%) and dark-light cycle (12 h) until experiments were carried out.

2.3. Biological assays

2.3.1. Determination of non-fasting blood glucose levels in normal rats

Male Sprague–Dawley rats (weight 230–260 g) were divided into groups of eight animals. One group, used as a control, received an isotonic saline solution, while the other groups received a decoction of *S. sonchifolius* leaves. The saline solution and the decoction were intraperitoneally (i.p.) injected (4 ml/kg body weight) or orally administered using a gastric tube (g.t.) (8 ml/kg body weight). Blood samples were obtained by amputation of the tail tip in non-fasting conditions at different times after the above treatments. Glycemia was determined using the glucose oxidase peroxidase enzymatic method (GT lab kit, Rosario, Argentina) by measuring optical density with a spectrophotometer adjusted to a 505 nm wavelength.

2.3.2. Glucose tolerance test in normal rats

Glucose tolerance tests (GTT) were carried out in male Sprague–Dawley rats. Distilled water (control), a reference drug (glymepiride), or the decoction of *S. sonchifolius* was i.p. administered to each eight-rat group. Thirty minutes later, a 50% glucose solution was applied subcutaneously (2 g/kg) to each rat. Blood samples were taken from the tail vein at 30 min (just before decoction administration), 0 h (just before glucose administration), and at 1, 2, 3, 4, 5, 6 and 7 h for the assay of plasma glucose. Glycemia was determined as described above.

2.3.3. Determination of non-fasting blood glucose levels in diabetic rats

Stable diabetes was induced by the administration of streptozotocin (STZ, Sigma Chemical Co., St Louis) 35 mg/kg (i.p.) dissolved in 10 mM sodium citrate buffer (pH 4.5) to male Sprague–Dawley rats; control rats received only citrate buffer. Diabetes was achieved within 24 h in the majority of animals, as determined by measuring daily non-fasting blood glucose and glucosuria. Only animals with blood glucose levels >350 mg/dl 2 days after STZ treatment were included in the study.

Diabetic animals were given an i.p. yacon leave decoction (4 ml/kg body weight) or an oral 2 % yacon leave tea ad libitum instead of water. Control diabetic animals received an i.p. isotonic solution or water ad libitum, respectively. Glycemia was determined as described above.

2.3.4. Insulin estimation

Plasma insulin levels were determined by means of the Abbott IMX MEIA method.

2.3.5. Creatinine clearance

Diabetic rats treated with 2% yacon leave tea for a 30 day period, diabetic untreated rats and control ones were placed in individual metabolic cages for 48 h. The first 24 h comprised an acclimatization period, after which a 24 h urine sample was collected and kept at 4°C. At the end of the collection period, blood samples were obtained. Serum and urinary creatinine was assessed by the Jaffé method using an Abbott Alcyon chemistry analyzer. Creatinine clearance, a measure of the rate of glomerular filtration, was calculated using standard formulae.

2.3.6. Microalbuminuria estimation

Rats were housed in metabolic cages for collection of urine as described above. Urinary albumin concentration was determined using Micral-Test II (Boheringer Mannheim GmbH, Mannheim, Germany) reactive strips.

2.4. Statistical analysis

Results were expressed as mean $\pm$ SD. The significance of the differences between the mean of the tests and the control studies was established by Student's t-test. P-values lower than 0.05 were considered to be significant.

3. Results

3.1. Effect of yacon decoction on non-fasting plasma glucose levels in normal rats

The effect of yacon on the non-fasting plasma glucose levels is shown in Fig. 1. The mean blood glucose levels of rats after the i.p. administration of the decoction were compared with the values in control rats, which received an isotonic saline solution. Basal glycemic level of control animals was 1.14 ± 0.10 g/l (Fig. 1A). There was no statistical difference in the initial basal glycemic levels between the studied groups. The plasma glucose level gradually decreased 1 h after i.p. administration of a 4 ml/kg of yacon decoction (Fig. 1B), reaching a minimum value 3 h after treatment (0.7 ± 0.14 g/l). The injection of the decoction produced a decrease in plasma glucose levels, which are significantly lower than those of the control group at 3 and 4 h after the administration. After treatment for 6 h glycemic levels returned to their baseline values.

A group of animals received an 8 ml/kg of yacon decoction through a gastric tube (Fig. 1C). Glycemic levels gradually decreased 2 h after the administration of the decoction. The minimum value of plasma glucose, 0.68 ± 0.09 g/l, was reached 4 h after treatment. The hypoglycemic effect was statistically significant from 3 to 5 h. The plasma glucose levels of treated rats reached the level of normal rats 6–7 h after treatment.

No significant changes in glycemic levels were found when normal glycemic rats received 2% tea up to 6 h after oral administration using a gastric tube (Fig. 1D), similar results being obtained when drinking water was completely replaced by tea and glucose levels were daily estimated during a wee. Two percent yacon tea did not significantly modify normal glycemia.

3.2. Effect of yacon decoction on transiently hyperglycemic rats

The plasma glucose levels of the control rats showed the highest increment in plasma glucose levels 1 h after the oral administration of glucose. Then, glycemia decreased gradually to the pre-glucose load level (Fig. 2). The decoction of yacon at a dose of 8 ml/kg (i.p.) produced a decrease in plasma glucose levels, which are significantly lower than those of the control group 3 h after glucose administration. Glymepiride (5 mg/kg, i.p.) produced a significant decrease in plasma glucose levels 2–3 h after glucose administration.

3.3. Effect of yacon tea on diabetic rats

In the STZ-induced diabetic rats, plasma glucose levels were 3.7 times higher than those in normal rats. The water decoction intraperitoneally injected in a single dose (4 ml/kg) or the single gastric tube administration of yacon decoction (8 ml/kg) to diabetic rats did not significantly reduce the plasma glucose levels (data not shown).

Yacon tea was administered ad libitum instead of water to diabetic rats for 30 days and the non-fasted plasma glucose level was determined. This treatment produced a significant decrease in glucose level compared with diabetic controls from the 3rd day until the end of the experimental period of the treatment. The maximum effect was observed at day 5 (3.00 ± 0.51 g/l for the yacon treated diabetic group as against 4.88 ± 0.35 g/l for the control diabetic group). At this point the glucose level was approximately 50% lower than the pretreatment one. A slight increase in plasma glucose level was observed from days 6 to 30. The diabetic control group showed an increase in plasma glucose as from day 4 of treatment.

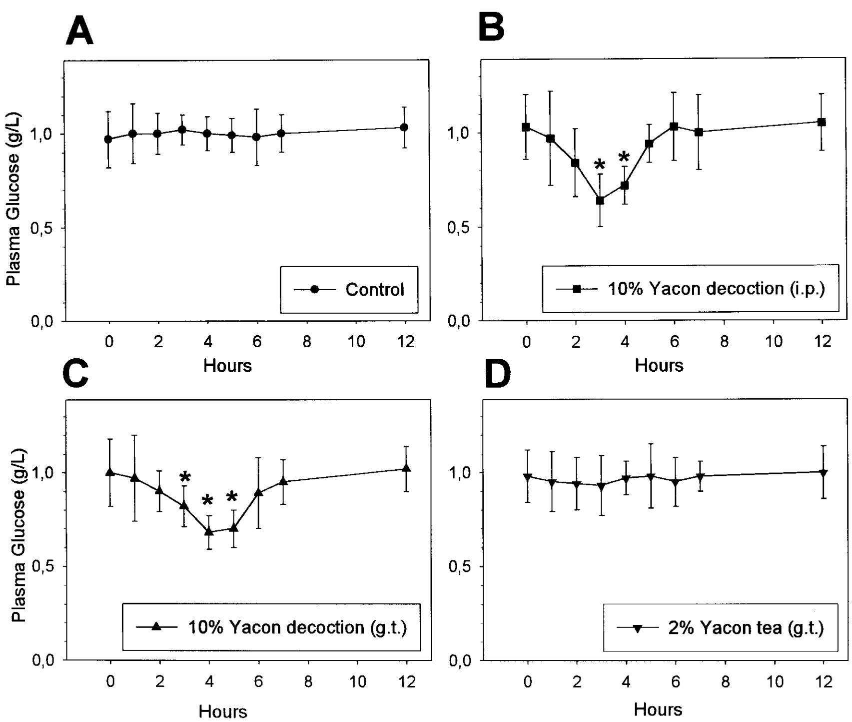

Fig. 1. Effect of the administration of different water extracts of *Smallantus sonchifolius* (yacon) on the non-fasting plasma glucose levels in normal rats. (A) Control animals. (B) Animals with 10% yacon decoction (i.p.). (C) Animals with 10% yacon decoction (gastric tube). (D) Animals with gastric tube 2% yacon tea (gastric tube). Curves are shown individually so as to make interpretation easier. Data are the mean ± SD from three different experiments. Each experiment was performed into groups of eight rats. * $P < 0.05$ compared with control.

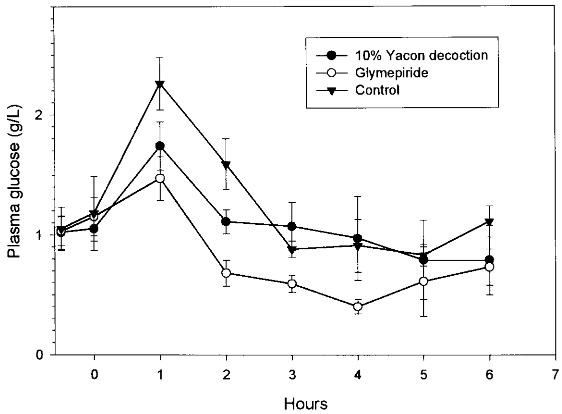

Fig. 2. Effect of yacon water decoction on the non-fasting glucose levels during glucose tolerance test in normal rats. Animals received a 10% yacon decoction by gastric tube 30 min after a 50% glucose solution was applied subcutaneously. Data are the mean ± SD from three different experiments. Each experiment was performed into groups of eight rats. * $P < 0.05$ compared with control.

The effect of ad libitum yacon tea administration to STZ-diabetic rats on plasma insulin levels is also shown in Fig. 3. The plasma insulin level was 1.0 ± 0.18 μU/ml in the STZ-induced diabetic rats while in control animals it was 6.8 ± 0.27 μU/ml throughout the experiment. In the diabetic rats that received yacon tea instead of water, insulin plasma levels increased slightly, reaching 3.3 ± 0.3 μU/ml at day 30 of treatment.

Renal damage is a well-known consequence of diabetes. Diabetic rats grew poorly and had significantly lower body weights than control and yacon-treated rats (Table 1). Renal hypertrophy in STZ-injected rats was ameliorated by yacon tea treatment. Diabetic rats exhibited increased creatinine clearance compared with controls. Yacon tea treatment improved creatinine clearance in diabetic animals. Control diabetic rats exhibited urinary albumin excretion at the end of the experimental period. In contrast, no urinary albumin could be detected in yacon-treated diabetic rats or in normal controls.

4. Discussion

The aim of this paper is to study the hypoglycemic activity of *S. sonchifolius* (yacon) leaves in rats as well as to provide an introductory approach for the evaluation of its traditional preparation in order to scientifically validate the

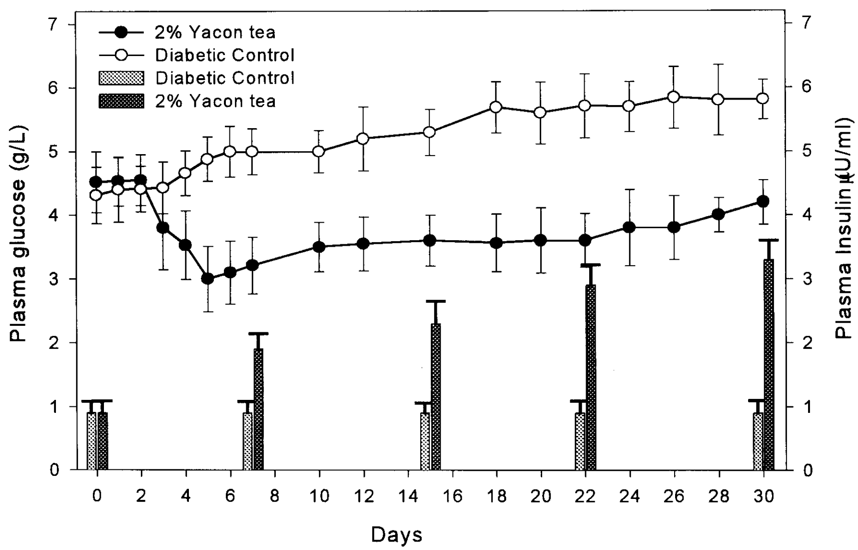

Fig. 3. Effect of the administration of 2% yacon tea ad libitum for 30 days on non-fasting plasma glucose levels (line plot) and non-fasting plasma insulin levels (bar plot). Data are the mean ± SD from three different experiments. Each experiment was performed into groups of eight rats.

Table 1
Effect of 30 day administration of yacon tea on STZ-induced diabetic rat[a]

Rats	Body weight (g)	Kidney weight	KW/BW ratio	Plasma glucose (g/l)	Creatinine clearance (ml/min)	UAE (mg/day)	Insulin (μU/ml)
Control	384.8 ± 26.9	1.34 ± 0.05	0.0035 ± 0.0002	1.01 ± 0.14	0.74 ± 0.04	N.D.	6.8 ± 0.27
Diabetic	225.6 ± 44.0	0.91 ± 0.07	0.0040 ± 0.0002	5.81 ± 0.31	1.26 ± 0.16	58.57 ± 16.25	1.0 ± 0.27
Diabetic + yacon	288.3 ± 9.1*	1.06 ± 0.10*	0.0036 ± 0.0003*	4.20 ± 0.35*	0.91 ± 0.05*	N.D.	3.3 ± 0.3

[a] The values represent the mean ± SD; * $P < 0.05$, compared with diabetic control group; UAE, urinary albumin excretion; N.D, not detected.

therapeutic properties of these plants in the control of diabetes. To the best of our knowledge, this is the first report that analyzes such hypoglycemic activity. Our results revealed that a single intraperitoneal injection or gastric tube administration of the yacon decoction caused a decrease in plasma glucose levels in normal rats, while the gastric tube administration of 2% yacon tea failed to produce such a decrease. It is possible that a higher dose of the water extract of yacon might cause the desired effect, in which case hypoglycemic activity would be a dose-dependent event.

STZ-induced hyperglycemia has been described as a useful experimental model to study the activity of hypoglycemic agents (Junod et al., 1969; Ledoux et al., 1986). Our results show that the intraperitoneal administration of STZ (35 mg/kg) effectively induced diabetes in normal non-fasted rats as reflected by glycosuria, high glycemia, polyphagia, polydypsia and body weight loss compared with normal control rats. The administration of 2% yacon tea for a 30 day period significantly inhibited the hyperglycemic action of STZ. Diabetic manifestations in yacon-tea-treated rats were reduced as revealed by clinical parameters. This effect was found only after 30 days, possibly because the hypoglycemic substance requires a certain period in order to reach the appropriate concentration in the body of the treated animals. A similar observation was reported by Alarcon-Aguilar et al. (1998) when analyzing numerous plants used as antidiabetic agents in Mexico.

Yacon decoction proved to have a hypoglycemic effect on healthy, transiently hyperglycemic and diabetic rats, a fact that led us to suppose that a certain pancreatic activity is necessary for such an effect to occur. Recently, Peungvicha et al. (1998) demonstrated that the water extract of *Piper sarmentosum* was able to decrease glucose levels in transiently hyperglycemic but not in diabetic rats (STZ dose, 75 mg/kg). In our case, it is probable that the use of a lower STZ dose produced an incomplete destruction of pancreatic β-cells even though rats became permanently diabetic.

Our results revealed that yacon decoction caused a significant decrease in the hyperglycemic peak during the glucose tolerance test as the reference drug glymepiride did. We found that a 30 day administration of 2% yacon tea increased circulating insulin levels. This increase may be a consequence of the stimulation of insulin synthesis and secretion, of the inhibition of insulin degradation or of both, since many compounds present in plants have been demonstrated to produce these effects. For instance, benzoic acid related molecules inhibited insulinase and enhanced insulin effects (Marles and Farnsworth, 1995; Peungvicha et al., 1998).

In diabetes there is a relationship between glucose homeostasis and renal damage (Rasch, 1979a,b), and the early identification of microalbuminuria is considered to be clinically relevant (Gomes et al., 1997). This fact is very important because many reports have demonstrated that therapeutical intervention can delay the development of end-stage renal disease (Mathiesen et al., 1994). In the present study we have shown that yacon tea treatment improves the general condition of diabetic rats and tends to restore to normal certain renal parameters, although toxicological studies have not been made. Throughout this study we demonstrated the hypoglycemic effect of the water extracts of *Smallantus sonchifolius* leaves in rats. However, the nature of the molecule/s responsible for such an effect requires further investigation.

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