

Aqueous extracts of husks of *Plantago ovata* reduce hyperglycaemia in type 1 and type 2 diabetes by inhibition of intestinal glucose absorption

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Plantago ovata has been reported to reduce postprandial glucose concentrations in diabetic patients. In the present study, the efficacy and possible modes of action of hot-water extracts of husk of *P. ovata* were evaluated. The administration of *P. ovata* (0.5 g/kg body weight) significantly improved glucose tolerance in normal, type 1 and type 2 diabetic rat models. When the extract was administered orally with sucrose solution, it suppressed postprandial blood glucose and retarded small intestinal absorption without inducing the influx of sucrose into the large intestine. The extract significantly reduced glucose absorption in the gut during *in situ* perfusion of small intestine in non-diabetic rats. In 28 d chronic feeding studies in type 2 diabetic rat models, the extract reduced serum atherogenic lipids and NEFA but had no effect on plasma insulin and total antioxidant status. No effect of the extract was evident on intestinal disaccharidase activity. Furthermore, the extract did not stimulate insulin secretion in perfused rat pancreas, isolated rat islets or clonal β cells. Neither did the extract affect glucose transport in 3T3 adipocytes. In conclusion, aqueous extracts of *P. ovata* reduce hyperglycaemia in diabetes via inhibition of intestinal glucose absorption and enhancement of motility. These attributes indicate that *P. ovata* may be a useful source of active components to provide new opportunities for diabetes therapy.

***Plantago ovata*: Glucose absorption: Gastrointestinal motility: Insulin secretion: Insulin action**

Diabetes mellitus is a major cause of disability and hospitalization resulting in significant financial and social burden across the world (Foster, 1994). Although a sub-group of type 2 patients can be managed by diet alone, most individuals with diabetes require oral hypoglycaemic drugs or insulin. However, the effectiveness of drug therapy is limited and is often associated with complications and side-effects including hypoglycaemia (Davis & Granner, 1996). Many patients fail to respond to oral antidiabetic agents and consequently need insulin therapy. In recent years, the popularity of complementary medicine has increased. Dietary measures and traditional plant therapies as prescribed by Ayurvedic and other indigenous systems of medicine, are used commonly in India (Warier, 1995). WHO has also recommended evaluation of the effectiveness of these plants in situations where there is a lack of safe modern drugs (Upadhyay & Pandey, 1984). The antihyperglycaemic activity of a large number of these plants has been evaluated and confirmed in different animal models (Swanston-Flatt *et al.* 1991).

Plantago ovata (Psyllium) is found in India, Iran, northern Africa and Pakistan. It has been used traditionally for constipation, diarrhoea, haemorrhoids, irritable bowel syndrome, weight loss, obesity, high cholesterol and diabetes (Mehta *et al.* 1976). The seeds and the husks contain high levels of fibre and become highly gelatinous when soaked in water. This stimulates bowel evacuation and thus has been used widely as a fibre supplement in the treatment of constipation

(Chopra *et al.* 1986). According to a report by the American Diabetic Association, fibre improves the control of blood glucose and delays glucose absorption and hyperinsulinaemia (Chandalia *et al.* 2000). Studies on the effect of *P. ovata* husk in patients with type 2 diabetes found that it can reduce the postprandial rise of glucose and insulin levels significantly (Wolever *et al.* 1991; Anderson *et al.* 1999). The plant has been shown also to reduce carbohydrate absorption (Abraham & Mehta, 1988). It delayed gastric emptying and reduced colon transit time in man (Washington *et al.* 1998).

It is well known that type 2 diabetes is associated with a significantly increased risk of macrovascular disease (Laakso & Lehto, 1997). Supplementation of the diet with soluble fibre or consumption of a high-fibre diet has been shown to lower total serum cholesterol and triacylglycerol in type 2 diabetic patients (Vinik & Jenkins, 1988). *P. ovata* also reduced total cholesterol and LDL-cholesterol in animals (Fernandez *et al.* 1995; Terpstra *et al.* 2000) and in man (Romero *et al.* 1998; Burton & Manninen, 1982).

The present study was undertaken to evaluate the antidiabetic properties of the husk of *P. ovata* and to explore the possible mechanisms of action. The effects of the plant on glucose homeostasis, carbohydrate digestion, absorption and gastrointestinal motility were investigated. Possible effects on insulin secretion were also evaluated using different *in vitro* systems and glucose uptake was studied using 3T3 adipocytes.

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Materials and methods

Plant materials and preparation of extract

Husks of *P. ovata* were collected from a local market in Bangladesh (north-eastern region) and botanically authenticated with voucher specimens deposited in the National Herbarium, Bangladesh. For the preparation of hot-water extract, *P. ovata* husk (200 g) was boiled with distilled water (44 litres) for 1 h and filtered. The filtrate was centrifuged at 4000 rpm (1750 g) and the supernatant was collected and concentrated by rotary evaporator. The extract was finally freeze-dried (21 g).

Animals and induction of type 1 and 2 diabetes

Long-Evans male rats were bred at BIRDEM (Bangladesh) and maintained on 12 h light–dark cycle at $21 \pm 2^\circ\text{C}$. A standard pellet diet and water were supplied *ad libitum*. The overall nutrient composition of the diet was 36.2% carbohydrate, 20.9% protein, 4.4% fat and 38.5% fibre with metabolizable energy content of 11.8 MJ/kg (2820 kcal/kg). Type 1 diabetes was induced by a single intraperitoneal injection of anaesthetized, fasted rats (180–220 g) with 65 mg streptozotocin/kg body weight dissolved, immediately before use, in 0.5 M-citrate buffer (pH 4.5). The blood glucose level was checked on the seventh day after injection of streptozotocin. Animals having blood glucose levels >20 mmol/l were considered to be diabetic. Type 2 diabetes was induced by a single intraperitoneal injection of rats 48 h old with 90 mg streptozotocin/kg body weight (Bonner-Weir *et al.* 1981). Experiments were carried out 3 months after injection. During the experimental periods, the diabetic rat models did not receive any therapy to control diabetes other than aqueous extracts of *P. ovata*. In addition, the mean fasting plasma glucose concentrations recorded in type 1 and type 2 diabetic rat models prior to acute studies were 9.0 (SEM 0.5) and 26.6 (SEM 1.0) mmol/l, respectively (n 6; $P < 0.001$).

Effects of aqueous extracts of Plantago ovata on glucose homeostasis

To evaluate effects on fasting blood glucose, the hot-water extract of *P. ovata* (0.5 g/kg body weight) was suspended in water and administered by gavage to 12 h fasted rats. The control group received an equal volume of deionized water. Serum was separated by centrifugation and stored at -20°C until analysed. Effects on glucose tolerance were similarly evaluated by administration of hot-water extracts together with glucose (2.5 g/10 ml per kg body weight) after a 12 h fast. Control rats received glucose solution alone. To evaluate chronic effects of *P. ovata*, type 2 diabetic rats were given hot-water extract (0.5 g/kg body weight by gavage) twice daily for 28 d. Control rats were similarly administered water alone (10 ml/kg body weight). Blood samples were collected from the cut tip of the tail at the times indicated in the figures. Serum was separated by centrifugation and stored at -20°C until analysed.

Effects of Plantago ovata on sucrose absorption from gastrointestinal tract

Type 2 diabetic and control rats were fasted for 12 h before receiving a 50% sucrose solution by gavage (2.5 g/kg body

weight) with or without hot-water extract of *P. ovata* (0.5 g/kg body weight). Blood samples were obtained from the tail vein before and 30, 60, 120 and 240 min after sucrose administration for the determination of glucose. Some of the rats were killed at these timings. The gastrointestinal tract was excised and divided into six segments: the stomach; the upper 20 cm, middle and lower 20 cm of the small intestine; the caecum; the large intestine. Each segment was washed out with acidified ice-cold saline and centrifuged at 3000 rpm (1000 g) for 10 min. The resulting supernatant was boiled for 2 h to hydrolyse the sucrose followed by neutralization with NaOH. Blood glucose and the amount of glucose liberated from residual sucrose in the gastrointestinal tract were measured. The gastrointestinal sucrose content was calculated from the amount of liberated glucose (Goto *et al.* 1995).

Effects of Plantago ovata on intestinal glucose absorption

An intestinal perfusion technique (Swintosky & Pogonowska-wala, 1982) was used to study the effect of *P. ovata* on intestinal absorption of glucose in 36 h fasted non-diabetic rats anaesthetized using sodium pentobarbital (50 g/kg). The hot-water extract of *P. ovata* (10 mg/ml, equivalent to 0.5 g/kg) suspended in Krebs Ringer buffer, supplemented with glucose (54 g/l), was passed through pylorus and the perfusate was collected from a catheter inserted at the end of ileum. The control group was perfused with Krebs Ringer buffer supplemented with only glucose. Perfusion was carried out at a rate of 0.5 ml/min for 30 min at 37°C . The results were expressed as percentage of absorbed glucose, calculated from the amount of glucose in solution before and after the perfusion.

Effects of Plantago ovata on intestinal disaccharide activity and gastrointestinal motility

The hot-water extract of *P. ovata* was administered by a gavage (0.5 g/kg body weight) to 20 h fasted rats. After 60 min, the rats were killed and the small intestine was isolated, cut longitudinally, rinsed with ice-cold saline and homogenized with 10 ml saline (0.9% NaCl). Aliquots of homogenate were then incubated with 40 mmol/l sucrose at 37°C for 1 h. Disaccharidase activity was calculated by glucose concentration converted from sucrose as $\mu\text{mol/mg}$ glucose per protein per h. For determination of gastrointestinal motility, the hot-water extract of *P. ovata* was given by gavage (0.5 g/kg body weight) to 12 h fasted non-diabetic rats. After 60 min, BaSO₄ milk (10% w/v in 0.5% sodium carboxymethyl cellulose suspension) was similarly administered. After a further 15 min, the rats were killed and gastrointestinal tract was excised. The distance traversed by BaSO₄ milk was measured and expressed as a percentage of the total length of small intestine.

Effects of Plantago ovata on insulin secretion and action

Long-Evans rats (180–250 g) were used for studies on insulin secretion from perfused pancreas and isolated islets. Pancreatic perfusion studies were carried out at 37°C according to the method of Giroix *et al.* (1983). Pancreatic islets were isolated by collagenase digestion (Moskalewski, 1969) and hot-water

extract of *P. ovata* was tested at 30 µg/ml. BRIN-BD11 cells were used to evaluate the effects on insulin secretion from a pure cellular population. The production and characteristics of these cells have been described in detail elsewhere (McClenaghan *et al.* 1996). The glucose concentrations employed for pancreatic perfusion and islet studies were 3 and 11 mmol/l. For insulin release studies using BRIN-BD11 cells, the acute tests were carried out at 5.6 mmol/l glucose. The effects of *P. ovata* on cellular glucose uptake also employed a cell line, namely 3T3-L1 cells obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Glucose uptake was measured by adaptation of the method of Frost & Lane (1985).

Analysis

Glucose was measured by the glucose oxidase phenol and 4-amino-antipyrine method, HDL-cholesterol, NEFA and total antioxidant status were determined by enzymatic colorimetric methods using commercial kits from SERA PAK (Berkeley, CA, USA). Serum fructosamine was determined by a colorimetric method using a kit from Boehringer Mannheim GmbH (Mannheim, Germany). Insulin was measured by ELISA using a rat insulin kit from Crystal Chem Inc. (Downers Grove, IL, USA). Hepatic glycogen was extracted (Vander Vries, 1954) and measured at 650 nm in a microwell plate ELISA reader (EL 340; Bio-Tek, Winooski, VT, USA). Platelet aggregation was measured using a Chrono Log Lumi aggregometer (Chronolog Corp., Havertown, PA, USA) linked to a potentiometric recorder. Results are presented as means and standard deviations. Groups of data were compared using unpaired Student's *t* test and Mann-Whitney U-test where appropriate. Where data were collected over a number of time-points, they have been analysed using repeated measures ANOVA, with Bonferroni adjustment to ensure an overall error rate of 5%. One-way ANOVA was performed and pair-wise comparisons to the control group were made using Dunnett's test to preserve an overall error rate of 5%. Differences were considered significant at $P < 0.05$.

Results

Acute and chronic effects of *Plantago ovata* on serum glucose and metabolic parameters

Administration of *P. ovata* in the fasting state did not exert any hypoglycaemic action in either non-diabetic or diabetic (type 1 and type 2) rats (Fig. 1(A–C)). When given simultaneously with an oral glucose load, *P. ovata* significantly opposed the rise of serum glucose at 30 min ($P < 0.01$) in controls, type 1 and type 2 diabetic rats (Fig. 1(D–F)). Oral administration of sucrose caused a prominent elevation of serum glucose with a peak at 30 min in both normal and type 2 diabetic rats (Fig. 2). The rise in blood glucose after sucrose loading was suppressed significantly by *P. ovata* at 30 and 60 min in both groups of rats ($P < 0.05$). As shown in Table 1, oral administration of *P. ovata* to type 2 diabetic rats for 28 d lowered fructosamine levels with significantly ($P < 0.05$) compared with controls. No significant differences were observed in fasting levels of serum glucose, insulin

and total antioxidant status. However, *P. ovata* significantly lowered total cholesterol ($P < 0.05$), triacylglycerol ($P < 0.05$) and NEFA ($P < 0.01$) levels. There were no significant differences in HDL, platelet aggregation, pancreatic insulin or hepatic glycogen content compared with the control (Table 1).

Effects of *Plantago ovata* on sucrose absorption from the gastrointestinal tract

Administration of hot-water extract of *P. ovata* (0.5 g/kg) with the sucrose load in non-diabetic rats increased the residual intestinal sucrose content significantly ($P < 0.01$) in the middle part of the intestine at 30 min (control *v.* *P. ovata*, 8.5 (SD 3.0) mg *v.* 18.8 (SD 6.2) mg) and in the entire small intestine at 60 min (upper 20 cm, 4.8 (SD 2.6) mg *v.* 15.1 (SD 6.8) mg; middle, 0.61 (SD 6.15) mg *v.* 15 (SD 7.0) mg; lower 20 cm, 1.1 (SD 0.6) mg *v.* 1.9 (SD 1.3) mg) and 120 min (1.6 (SD 0.1–0) mg *v.* 5.5 (SD 2.8) mg, 4.7 (SD 1.9) mg *v.* 12.1 (SD 4.2) mg and 0.7 (SD 0.32) mg *v.* 1.6 (SD 0.64) mg). The total sucrose content remaining in the gastrointestinal tract was increased significantly in *P. ovata*-treated rats compared with normal controls ($P < 0.05$; Fig. 3(A)). Similar effects of *P. ovata* were observed in type 2 diabetic rats after a sucrose load ($P < 0.05$, at 60 and 120 min; Fig. 3(B)).

Effects of *Plantago ovata* on intestinal glucose absorption

As shown in Fig. 4, intestinal glucose absorption in non-diabetic rats was almost constant during 30 min of perfusion. Addition of *P. ovata* to the glucose perfusate resulted in a substantial decrease in intestinal glucose absorption during the whole experimental period ($P < 0.01$).

Effects of *Plantago ovata* on intestinal disaccharidase activity and gastrointestinal motility

There were no significant differences on disaccharidase (sucrase) activity between non-diabetic controls and rats supplemented with *P. ovata* (data not shown). In contrast, the plant extract significantly increased gastrointestinal motility by 20%, assessed using BaSO₄ milk, compared with non-diabetic controls ($P < 0.001$).

Effects of *Plantago ovata* on insulin secretion and action

Hot-water extract of *P. ovata* did not affect insulin secretion from the perfused rat pancreas, isolated rat islets or clonal pancreatic β cell line, BRIN-BD11, at a range of concentrations tested (8, 40, 200, 1000 and 5000 µg/ml) (data not shown). Similarly, *P. ovata* did not affect glucose transport in 3T3 adipocytes in the absence or presence of 10⁻⁹ M-insulin (data not shown).

Discussion

Plantago ovata is commonly used in India, Pakistan and Bangladesh for the treatment of constipation, irritable bowel syndrome and diabetes. However, a very limited number of studies have evaluated antihyperglycaemic effects of the husk (Anderson *et al.* 1999). In the present study, the effects of hot-water extract of *Plantago ovata* on glucose homeostasis

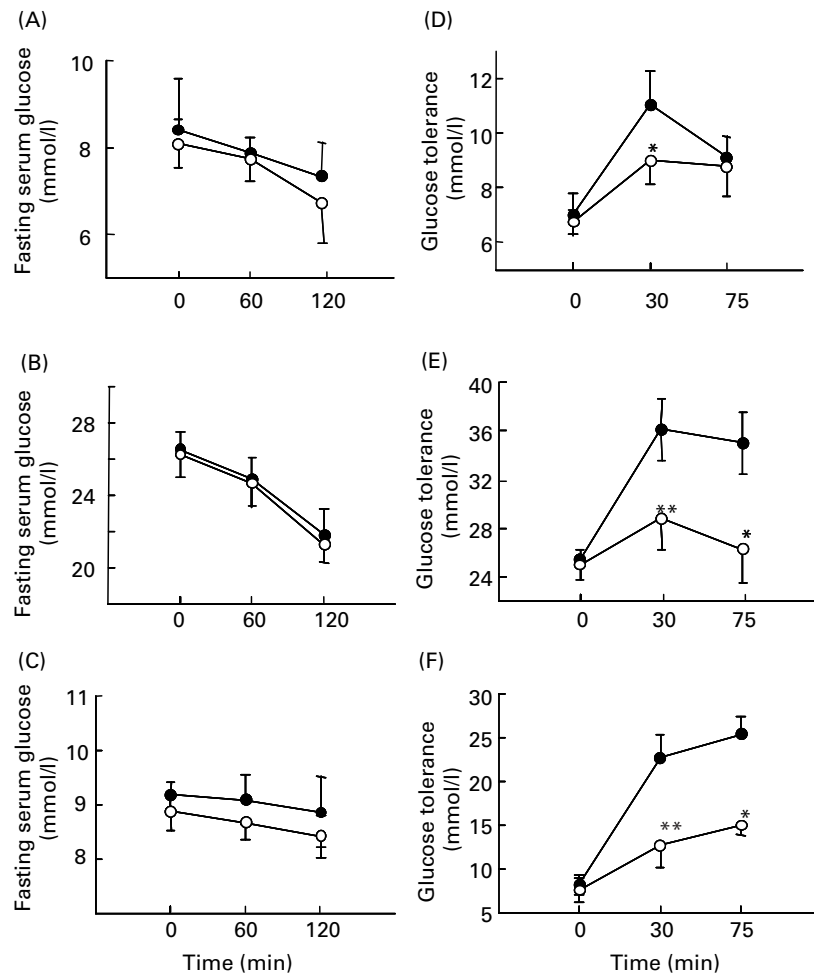


Fig. 1. Effects of hot-water extracts of *Plantago ovata* on fasting serum glucose (A–C) and glucose tolerance (D–F) in non-diabetic (A, D), type 1 diabetic (B, E) and type 2 diabetic (C, F) rats. Fasting rats were given glucose (2.5 g/kg body weight) without (●) or with (○) hot-water extract of *P. ovata* (0.05 g/kg body weight). For details of procedures, see p. 132. Values are means with standard deviations depicted by vertical bars (n 6). Mean values were significantly different from those of the respective control group (repeated measures ANOVA, adjusted using a Bonferroni correction): * P <0.05; ** P <0.01.

were evaluated using a number of model *in vivo* and cellular systems.

Postprandial hyperglycaemia is undesirable as it increases glycosylation products, such as methylglyoxal, which play a role in the development of diabetic vascular disease (Thornalley, 1996). Acute elevation of glucose also increases coagulation (Ceriello *et al.* 1996) and results in multiple disturbances in endothelial cell function (Haller, 1997; King *et al.* 1997). The present serum fructosamine data in type 2 diabetic rat models receiving *P. ovata* extract daily clearly demonstrate that the plant exhibits antihyperglycaemic properties in the previous 2–3 weeks. Unlike fasting glucose, which did not change serum fructosamine, it represents a stable measure that reflects the recent glycaemic environment.

When administered with an oral glucose load, *P. ovata* markedly improved glucose tolerance in normal rats and established models of type 1 and type 2 diabetes. The antihyperglycaemic action of the extract in severely insulin-deficient type 1 diabetic rats argues against the action being mediated by increased insulin secretion. This was confirmed by lack of the effect of 28 d treatment of type 2 rats on circulating insulin as well as *in vitro* insulin secretion studies with

isolated perfused rat pancreas, isolated rat islets and clonal BRIN-BD11 cells. Furthermore, *P. ovata* did not affect glucose transport in 3T3 adipocytes. This indicates that enhancement of insulin sensitivity or glucose-lowering ‘insulin-like’ action is also unlikely to account for antidiabetic activity of the plant extract.

Since the glucose-lowering effect of *P. ovata* was clearly evident when simultaneously administered with glucose, inhibition of glucose absorption in the gut is a likely contributor to the mechanism of action (Lempcke, 1987; Vinik & Wing, 1990). It is well known that high-fibre diets improve glucose tolerance in diabetes (Fukagawa *et al.* 1990; Nutall, 1993). This effect may be due to retarded gastric emptying, increased intestinal transit, or modification of the secretion and action of digestive enzymes (Hannah & Howard, 1994). In the present study, we assessed various effects of *P. ovata* extract on carbohydrate digestion and absorption in the gut. When the extract was given by gavage simultaneously with sucrose solution to non-diabetic and type 2 diabetic rats, it suppressed the resulting rise of serum glucose and increased the unabsorbed sucrose content throughout the small intestine. These effects do not appear to be associated with inhibition of intestinal

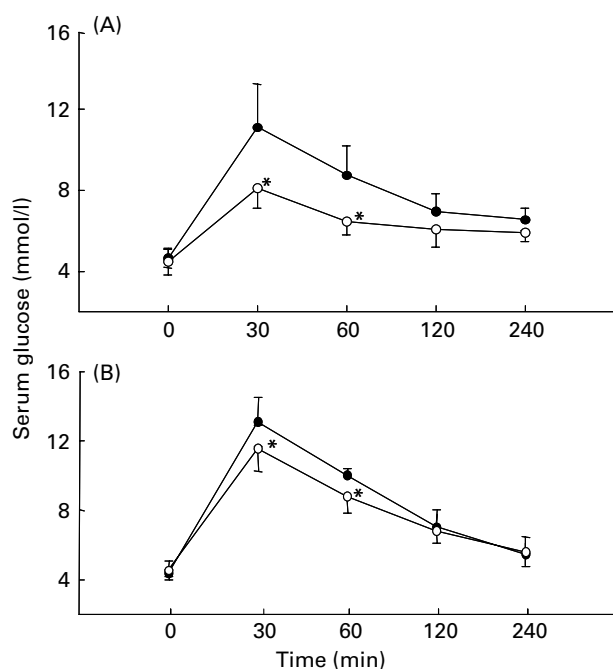


Fig. 2. Effects of hot-water extract of *Plantago ovata* on serum glucose after sucrose load in non-diabetic (A) and type 2 diabetic (B) rats. Rats were fasted for 20 h and administered a sucrose solution by gavage (2.5 g/kg body weight) without (●) or with (○) hot-water extract of *P. ovata* (0.5 g/kg body weight). For details of procedures, see p. 132. Values are means with standard deviations depicted by vertical bars (n 6). Mean values were significantly different from those of the respective control group (repeated measures ANOVA, adjusted using a Bonferroni correction): * P < 0.05.

disaccharidase activity, although loss of competitive effects on enzyme activity cannot be entirely ruled out. This suggests that reduction of sucrose absorption was not related to the enzyme activity as observed with α -glucosidase inhibitors (Hanefeld *et al.* 1991). However, the extract significantly

reduced glucose absorption during *in situ* perfusion of small intestine. Thus, limitation of the glycaemic excursion by *P. ovata* is at least partly due to the retardation of carbohydrate absorption, which is consistent with the suggestion of Abraham & Mehta (1988). Interestingly, several early *in vitro* studies suggest that high concentrations of metformin also inhibit glucose absorption (Caspary & Creutzfeld, 1971; Lorch, 1971). The effects of *P. ovata* extract on gastrointestinal motility were also evaluated in non-diabetic rats. A significant increase in motility was noted, which supports the findings of others (Chopra *et al.* 1986; Marteau *et al.* 1994). Thus, a component of the antihyperglycaemic activity of *P. ovata* is probably due to increased motility of the gastrointestinal tract.

Dyslipidaemia, particularly low levels of HDL-cholesterol and high levels of total cholesterol, triacylglycerols and NEFA, is an important risk factor for atherosclerotic complications of diabetes (Laakso & Lehto, 1997). Elevated NEFA levels also lead to pancreatic β cell lipid overload, dysregulation of insulin secretion (Prentki *et al.* 1992; Zhou & Grill, 1995) and apoptotic cell death (Maedler *et al.* 2001; Lupi *et al.* 2002). Raised NEFA contributes to many of the other major metabolic abnormalities in diabetes including decreases in glucose transport, glycogen synthesis and glucose oxidation (DeFronzo *et al.* 1992). Thus, a key goal in the management of diabetes is correction of dyslipidaemia (Vague, 2003). In the present study, administration of extract of *P. ovata* for 28 d lowered total cholesterol, triacylglycerol and NEFA levels in type 2 diabetic rats. The present findings are consistent with other investigations (Everson *et al.* 1992; Fernandez *et al.* 1995). In the present chronic study, there was no significant effect on glycogen deposition in the liver, which may reflect lack of effect of *P. ovata* on insulin secretion.

In conclusion, the present study has demonstrated that the hot-water extract of the husk of *P. ovata* exerts strong antihyperglycaemic actions in type 1 and type 2 diabetes by

Table 1. Effects of 28 d treatment with *Plantago ovata* on glucose homeostasis and other metabolic features in type 2 diabetic rats (n 12)[†]

(Values are means and standard deviations)

Parameters	Day 0				Day 28			
	Control		<i>P. ovata</i>		Control		<i>P. ovata</i>	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Glucose (mmol/lol per l)	7.0	0.9	7.3	0.8	7.1	0.6	6.7	0.9
Fructosamine (μ mol/l)	132.9	22.0	150.5	20.2	157.8	14.8	129.4*	14.1
Insulin (ng/ml)	0.44	0.09	0.41	0.07	0.46	0.14	0.47	0.08
Pancreatic insulin (nmol/g tissue)					0.79	0.24	0.81	0.51
Liver glycogen (g/100 g)					1.69	0.37	1.63	0.56
TAS (mmol/l)	0.8	0.1	0.9	0.1	0.8	0.1	0.9	0.2
Cholesterol (mg/dl)	710	110	702	104	712	101	627*	62
Triacylglycerol (mg/l)	513	84	562	52	495	98	404*	61
HDL-cholesterol (mg/l)					399	82	447	68
NEFA (mmol/l)	0.7	0.2	0.7	0.1	0.6	0.1	0.5*	0.1
Platelet aggregation (%)					40.1	3.6	36.3	4.7

TAS, total antioxidant status.

Mean values were significantly different from those of the control group (unpaired t test): * P < 0.05.

[†]Diabetes was induced by injection of neonatal rats with 90 mg streptozotocin/kg body weight 3 months prior to the experiment. Hot-water extract of *P. ovata* was administered by gavage (0.5 g/kg body weight) twice daily for 28 d. For details of procedures, see p. 132.

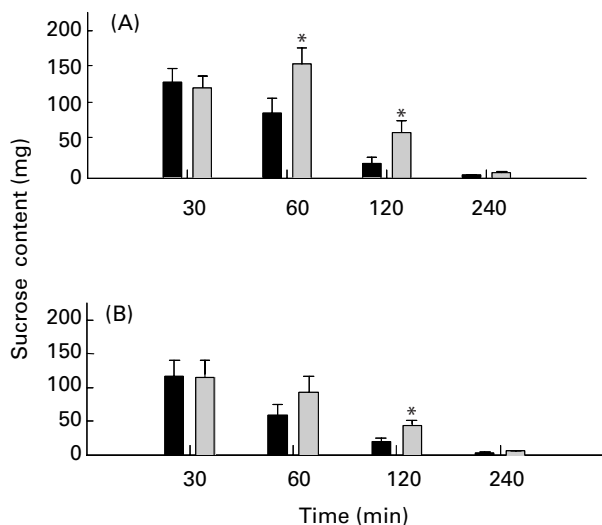


Fig. 3. Effects of hot-water extract of *Plantago ovata* on gastrointestinal sucrose content after oral sucrose loading in non-diabetic (A) and type 2 diabetic (B) rats. Rats were fasted for 20 h prior to administration of sucrose solution (2.5 g/kg body weight) by gavage without (■) or with (▒) hot-water extract of *P. ovata* (0.5 g/kg body weight). For details of procedures, see p. 132. Values are means with standard deviations depicted by vertical bars ($n = 6$). Mean values were significantly different from those of the respective control group (repeated measures ANOVA, adjusted using a Bonferroni correction): * $P < 0.05$.

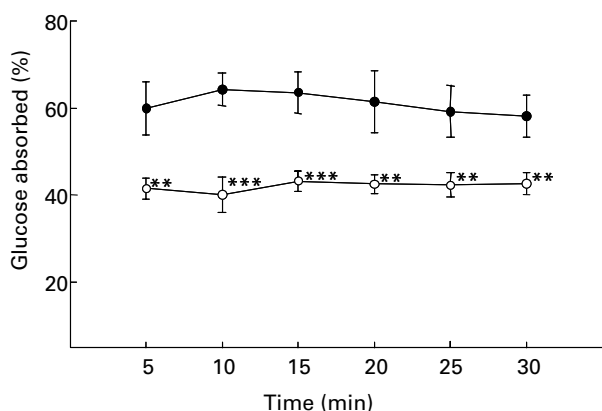


Fig. 4. Effects of hot-water extract of *Plantago ovata* on intestinal glucose absorption in non-diabetic rats. Rats were fasted for 36 h and intestine was perfused with glucose (54 g/l) with (○) or without (●) hot-water extract of *P. ovata* (10 mg/ml). For details of procedures, see p. 132. Values are means with standard deviations depicted by vertical bars ($n = 6$). Mean values were significantly different from those of the control group (repeated measures ANOVA, adjusted using a Bonferroni correction): ** $P < 0.01$; *** $P < 0.001$.

retarding the absorption of ingested carbohydrate. It also served to increase gastrointestinal motility and reduce atherogenic lipids. Thus *P. ovata* may be a useful dietary adjunct for the treatment of hyperglycaemia as well as dyslipidaemia in type 2 diabetes.

References

Abraham ZD & Mehta T (1988) Three-week psyllium husk supplementation: effect on plasma cholesterol concentrations, fecal steroid excretion, and carbohydrate absorption in men. *Am J Clin Nutr* **47**, 67–74.

Anderson JW, Allgood LD, Turner J, Oeltgen PR & Daggy BP (1999) Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia. *Am J Clin Nutr* **70**, 466–473.

Bonner-Weir S, Trend DF, Honey RN & Weir GC (1981) Responses of neonatal rat islets to streptozotocin: limited B-cell regeneration and hyperglycemia. *Diabetes* **30**, 64–69.

Burton R & Manninen V (1982) Influence of a psyllium-based fibre preparation on faecal and serum parameters. *Acta Med Scand* **668**, S91–S94.

Caspary W & Creutzfeld W (1971) Analysis of inhibitory effect of biguanides on glucose absorption: inhibition of active sugar transport. *Diabetologia* **7**, 379–385.

Ceriello A, Taboga C, Tonutti L, Giacomello R, Stel L, Motz E & Pirisi M (1996) Post-meal coagulation activation in diabetes mellitus: the effect of acarbose. *Diabetologia* **39**, 469–473.

Chandalia M, Garg A, Lutjohann D, Bergmann K, Grundy SM & Brinkley LJ (2000) Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* **342**, 1392–1398.

Chopra RN, Nayar SL & Chopra IC (1986) *Glossary of Indian Medicinal Plants (including the supplement)*. New Delhi: Council of Scientific and Industrial Research.

Davis SN & Granner DK (1996) Insulin, oral hypoglycaemic agents, and the pharmacology of endocrine pancreas. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed., pp. 1503 [JG Hardmen and LE Limbrid, editors]. New York: McGraw-Hill.

DeFronzo RA (1992) Pathogenesis of type 2 diabetes mellitus: a balance overview. *Diabetologia* **35**, 389–397.

Everson GT, Daggy BP, McKinley C & Story JA (1992) Effects of psyllium hydrophilic mucilloid on LDL-cholesterol and bile acid synthesis in hypercholesterolemic men. *J Lipid Res* **33**, 1183–1192.

Fernandez ML, Ruiz LR & Conde AK (1995) Psyllium reduces plasma LDL in guinea pigs by altering hepatic cholesterol homeostasis. *J Lipid Res* **36**, 1128–1138.

Foster DW (1994) Diabetes mellitus. In *Harrison's Principles of Internal Medicine*, pp. 1979–1981 [KJ Isselbacher, E Braunwald, JD Wilson, JB Martin, AS Fauci and DL Kasper, editors]. New York: McGraw-Hill.

Frost SC & Lane MD (1985) Evidence for the involvement of vicinal sulfhydryl groups in insulin-activated hexose transport by 3T3-L1 adipocytes. *J Biol Chem* **260**, 2646–2652.

Fukagawa NK, Anderson JW & Hageman G (1990) High-carbohydrate, high-fibre diets increase peripheral insulin sensitivity in healthy young and old adults. *Am J Clin Nutr* **52**, 524–528.

Giroix MH, Portha B, Kergoat M, Bailbe D & Picon L (1983) Glucose insensitivity and amino-acid hypersensitivity of insulin release in rats with non-insulin-dependent diabetes: a study with the perfused pancreas. *Diabetes* **32**, 445–451.

Goto Y, Yamada K, Ohyama T, Matsuo T, Odaka H & Ikeda H (1995) An alpha-glucosidase inhibitor, AO-128, retards carbohydrate absorption in rats and humans. *Diabetes Res Clin Pract* **28**, 81–87.

Haller H (1997) Postprandial glucose and vascular disease. *Diabet Med* **14**, S50–S56.

Hanefeld MFS, Schulze J, Spengler M, Wargenau M, Schollberg K & Fucker K (1991) Therapeutic potential of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. *Diabetes Care* **14**, 732–737.

Hannah JS & Howard BV (1994) Dietary fats, insulin resistance and diabetes. *J Cardiovasc Risk* **1**, 31–37.

King GL, Ishi H & Koya D (1997) Diabetic vascular dysfunction: a model of excess activation of protein kinase C. *Kidney Int* **52**, S77–S85.

Laakso M & Lehto S (1997) Epidemiology of macrovascular disease in diabetes. *Diabetes Rev* **5**, 294–315.

- Lembcke B (1987) Control of absorption: delaying absorption as a therapeutic principle. In *Structure and Function of the Small Intestine*, pp. 263–280 [WF Caspary, editor]. Amsterdam: Excerpta Medica.
- Lorch E (1971) Inhibition of intestinal absorption and improvement of oral glucose tolerance by biguanides in the normal and in the streptozotocin diabetic rat. *Diabetologia* **7**, 195–203.
- Lupi R, Dotta F, Marselli L, Del Guerra S, Masini M & Santangelo C (2002) Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: evidence that β cell death is caspase mediated, particularly dependent on ceramide pathway and Bcl-2 regulated. *Diabetes* **51**, 1437–1442.
- McClenaghan NH, Barnett CR, Ah-Sing E, Abdel-Wahab YH, O'Harte FP, Yoon TW, Swanston-Flatt SK & Flatt PR (1996) Characterization of a novel glucose-responsive insulin-secreting cell line, BRIN-BD11, produced by electrofusion. *Diabetes* **45**, 1132–1140.
- Maedler K, Spinas GA, Dyntar D, Moriz W, Kaiser N & Donath MY (2001) Distinct effects of saturated and monounsaturated fatty acids on β cell turnover and function. *Diabetes* **50**, 69–76.
- Marteau P, Flourie B, Cherbut C, Correze JL, Pellier P, Seylaz J & Rambaud JC (1994) Digestibility and bulking effect of ispaghula husks in healthy humans. *Gut* **35**, 1747–1752.
- Mehta KG, Modi R & Gupta R (1976) Psyllium. *Indian J Agron* **21**, 509–510.
- Moskalewski S (1969) Studies the culture and transplantation of isolated islets of langerhans of the guinea pig. *Proc K Ned Akad Wet C* **72**, 157–171.
- Nutall FO (1993) Dietary fibre in the management of diabetes. *Diabetes* **42**, 503–508.
- Prentki M, Vischer S, Glennon MC, Regazzi R, Deeney JT & Corkey BE (1992) Malonyl-CoA and long chain esters as metabolic coupling factors in nutrient-induced insulin secretion. *J Biol Chem* **267**, 5802–5810.
- Romero AL, Romero JE, Galviz S & Fernandez ML (1998) Cookies enriched with psyllium or oat bran lower plasma LDL cholesterol in normal and hypercholesterolemic men from Northern Mexico. *J Am Coll Nutr* **17**, 601–608.
- Swanston-Flatt SK, Day C, Flatt PR & Bailey CJ (1991) Evaluation of the antihyperglycaemic properties of traditional plant treatments for diabetes. In *Frontiers in Diabetes Research: Lessons from Animal Diabetes*, vol. 3, pp. 286–293 [E Shafir, editor]. London: Smith-Gordon and Company.
- Swintosky JV & Pogonowskawa E (1982) The in-situ rat gut technique. *Pharm Int* **3**, 163–167.
- Terpstra AH, Lapre JA, de Vries HT & Beynen AC (2000) Hypocholesterolemic effect of dietary psyllium in female rats. *Ann Nutr Metab* **44**, 223–228.
- Thornalley PJ (1996) Advanced glycation and the development of diabetic complications: unifying the involvement of glucose, methylglyoxal and oxidation stress. *Endocrinol Metab* **3**, 149–166.
- Upadhayay VP & Pandey K (1984) Ayurvedic approach to diabetes mellitus and its management by indigenous resources. In *Diabetes Mellitus in Developing Countries*, pp. 375–377 [JS Bajay, editor]. New Delhi: Blackwell Publishing.
- Vague P (2003) Is metformin more than an oral hypoglycaemic agent? *Diabetes Metab* **29**, 6S5–6S7.
- Vander Vries J (1954) Two methods for the determination of glycogen in liver. *Biochem J* **57**, 410–416.
- Vinik AL & Jenkins DJA (1988) Dietary fibre in management of diabetes. *Diabetes Care* **11**, 160–173.
- Vinik AL & Wing RR (1990) Dietary fibre in management of diabetes. In *Diabetes mellitus: Theory and Practice*, 2nd ed., pp. 465–497 [H Rifkin and D Porte Jr., editors]. New York: Elsevier.
- Warier PK (1995) *O basilicum* Linn. In *Indian Medicinal Plants*, pp. 160–163 [PK Warrier, VPK Nambia and C Ramankutty, editors]. Madras: Orient Longman.
- Washington N, Harris M, Mussellwhite A & Spiller RC (1998) Moderation of lactulose-induced diarrhea by psyllium: effects on motility and fermentation. *Am J Clin Nutr* **67**, 317–321.
- Wolever TM, Vuksan V, Eshuis H, Spadafora P, Peterson RD, Chao ES, Storey ML & Jenkins DJ (1991) Effect of method of administration of psyllium on glycemic response and carbohydrate digestibility. *J Am Coll Nutr* **10**, 364–371.
- Zhou YP & Grill V (1995) Long-term exposure to fatty acids and ketones inhibits B cell functions in human pancreatic islets of Langerhans. *J Clin Endocrinol Metab* **80**, 1584–1590.