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The effects of traditional antidiabetic plants on *in vitro* glucose diffusion

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Abstract

Plants represent a vast source of potentially useful dietary supplements for improving blood glucose control and preventing long-term complications in type 2 diabetes mellitus. Ten aqueous plant extracts with proven antihyperglycemic properties were examined at a concentration of 50g plant extract/l using an *in vitro* method to assess their possible effects on glucose diffusion across the gastrointestinal tract. *Agrimony eupatoria* (agrimony) and *Persea americana* (avocado) decreased glucose movement *in vitro* more than 50%. Aqueous extracts of *Agaricus campestris* (mushroom), *Coriandrum sativum* (coriander), *Eucalyptus globulus* (eucalyptus), *Juniperus communis* (juniper), *Medicago sativa* (lucerne), and *Viscum album* (mistletoe) decreased significantly glucose movement but were less effective than agrimony and avocado. *Urtica diocia* (nettle) and *Sambucus nigra* (elder) extracts did not significantly decrease glucose diffusion. The effects of agrimony, avocado, coriander and mushroom extracts were found to be concentration-dependent. These results suggest that part of the antihyperglycemic actions of these plants may be by decreasing glucose absorption *in vivo*.

Keywords: Traditional antidiabetic plants; Glucose diffusion; Dietary control

1. Introduction

Diabetes mellitus is characterised by hyperglycemia that is induced by decreased cellular glucose uptake and metabolism [1]. Control of plasma glucose concentrations is vital to

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decrease the incidence and severity of long-term diabetic complications [2]. Currently, dietary changes, oral hypoglycaemic agents, or insulin injections are utilised to prevent hyperglycemia. At present, drug therapies either alone or in combination cannot restore normal blood glucose homeostasis, and many limitations exist in their use [3]. While external insulin is necessary for control of type 1 diabetes mellitus, the use of drug therapy in type 2 diabetes is initiated only after dietary and lifestyle modifications [4].

Various dietary regimes have been considered for prevention of hyperglycaemia in diabetes [5]. Jenkins et al. [6] proposed the use of plant derived products containing high concentrations of dietary fibre and complex polysaccharides. Inclusion of viscous polysaccharides in the diet decreased postprandial blood glucose concentrations in subjects with type 2 diabetes [7]. In particular, guar gum has decreased postprandial blood glucose concentrations in several experiments [8]. However, the highly viscous and unpalatable nature of guar gum has limited its use in dietary management of type 2 diabetes [9].

More than 400 plants world-wide have been documented as beneficial in the treatment of diabetes [10]. The majority of traditional antidiabetic plants await proper scientific and medical evaluation for their ability to improve blood glucose control [3,11]. However, a few comprehensive studies of traditional antidiabetic plants have been carried out [12–14]. The antidiabetic actions of 37 European plants, traditionally used as adjuncts to the treatment of diabetes, were investigated by dietary administration to streptozotocin-treated mice and *db/db* mice [15]. These studies identified 21 plants with general beneficial effects, including 11 with significant antihyperglycemic activity [15].

Further studies with the most effective plants (Table 1) demonstrated that the antihyperglycemic activities were in part explained by the ability of water soluble plant components to increase glucose transport and metabolism in muscle and/or to stimulate insulin secretion [16–22]. To date no research has been carried out to evaluate the potential of these plants to additionally retard the diffusion and movement of glucose in the intestinal tract. The present study was undertaken to investigate the effects of 9 previously studied antidiabetic plants and *Persea americana* (avocado; Table 1) on glucose movement across dialysis membrane into external solution, which is a convenient model for assessing factors affecting glucose absorption *in vitro*.

2. Methods and materials

2.1. Plant materials and preparation of plant extracts

Dried material of 10 plants (*Agaricus campestris* (mushroom), *Agrimony eupatoria* (agrimony), *Coriandrum sativum* (coriander), *Eucalyptus globulus* (eucalyptus), *Juniperus communis* (juniper), *Medicago sativa* (lucerne), *Persea americana* (avocado), *Sambucus nigra* (elder), *Urtica diocia* (nettle), and *Viscum album* (mistletoe) were obtained from a commercial source in Birmingham (West Midlands, UK). These were homogenised to a fine powder and stored at room temperature (20 ± 2°C) in opaque screw-top jars. Aqueous extracts of plants were prepared by a method of infusion (elder, juniper, lucerne, mistletoe, mushroom, nettle) or decoction (agrimony, avocado, coriander, eucalyptus) as described

Table 1
Antidiabetic actions of selected traditional plant treatments for diabetes

Plant	Hyperglycaemia[1]	Glucose uptake and metabolism[2]	Insulin secretion[3]	[Reference]
Agaricus campestris (mushroom)	↓	↑	↑	[13,17]
Agrimony eupatoria (agrimony)	↓	↑	↑	[14,18]
Coriandrum sativum (coriander)	↓	↑	↑	[14,21]
Eucalyptus globulus (eucalyptus)	↓	↑	↑	[14,19]
Juniperus communis (juniper)	↓ ?	ND	↑	[3,14,30]
Medicago sativa (lucerne)	↓	↑	↑	[14,16]
Persea americana (avocado)	↓	ND	ND	[27]
Sambucus nigra (elder)	—	↑	↑	[13,21]
Urtica diocia (nettle)	?	ND	ND	[13, 32]
Viscum album (mistletoe)	—	ND	↑	[13,21]

Effect of plant: ↑, increase; ↓, decrease (beneficial effect on hyperglycaemia); ?, effect queried; ND, effect not determined.

[1] Effects on hyperglycaemia were demonstrated in streptozocin-diabetic mice given plant in their diet (6.25% w/w) and drinking water (0.25% w/v), with exception of avocado which used subjects with type 2 diabetes.

[2] Effects on glucose uptake and metabolism were demonstrated *in vitro* using isolated mouse abdominal muscle.

[3] Effects on insulin secretion were demonstrated *in vivo* using mice and/or *in vitro* using cultured BRIN-BD11 pancreatic B-cells. Beneficial actions *in vitro* were observed at plant extract concentrations of approximately 1 g/l and did not affect cellular viability.

previously [3,18]. In brief, for infusions 1 g of powdered material was placed in 40 ml of boiling (distilled) water, then removed from the heat source and allowed to infuse for 15 min. For decoctions, 1g of powdered plant material was placed in 40 ml of cold (distilled) water, boiled, removed from the heat source and allowed to infuse for 15 min. Each suspension was filtered (Whatman no. 1) and the volume readjusted to 40 ml with distilled water. Aliquots of extract (1 ml) were dried under vacuum (Savant speedvac; Savant Instrumentation Incorp., Framingdale, NY), stored at −20°C and reconstituted on the day of use with distilled water. Extract concentrations are expressed as g total plant material weight (rather than dry residue) per l of water.

2.2. Effects of plant extracts on glucose movement

A simple model system was used to evaluate effects of plant extracts on glucose movement *in vitro.* This model was adapted from a method described by Edwards et al. [23] which involved the use of a sealed dialysis tube into which 15 ml of a solution of glucose and NaCl (0.15 M) was introduced and the appearance of glucose in the external solution was measured. The model used in the present experiments consisted of a dialysis tube (6 cm × 15 mm; (Spectra/Por®, MWCO:2000) into which 2 ml of 0.15 M NaCl containing 0.22 mM D-glucose was added. The dialysis tube was sealed at each end and placed in a 50 ml

centrifuge tube (Iwaki Scitech Div., Japan) containing 45 ml of 0.15 M NaCl. The tubes were placed on an orbital shaker (Balart Products, USA) and kept at room temperature (20 ± 2°C). The movement of glucose into the external solution was monitored at set time intervals, as illustrated in the figures. In the first series of experiments, the effects of 50 g/l plant extracts on glucose diffusion were compared to control tests conducted in the absence of plant extract. At the end of the experimental period, the concentrations of glucose within the dialysis tubing were measured. A second experimental series investigated the concentration-dependent effects (6.25, 12.5, 25 and 50 g/l) of plant extracts that demonstrated the greatest inhibitory effects on glucose movement into the external solution. All tests were carried out in triplicate. Glucose concentrations were measured using the glucose oxidase method of analysis (Beckman Glucose Analyser II, Beckman Instruments, Inc., California).

2.3. Statistical analyses

Incremental areas under the glucose curves (AUC) were calculated using a computer program (CAREA) employing the trapezoidal rule [24]. Results are expressed as mean ± SEM, and glucose concentrations and AUC were compared with the control group using Student's unpaired *t* test. Groups of data were considered to be significantly different at $p < 0.05$.

3. Results

3.1. Effects of plant extracts on glucose diffusion in vitro

After 26 h without plant extract (control), glucose movement out of dialysis had reached a plateau with a mean glucose concentration in the external solution was 9.6 ± 0.3 mmol/l (Fig. 1). Agrimony and avocado extracts were the most potent inhibitors of glucose movement in the model system. In the presence of agrimony extract (50 g/l) glucose diffusion was significantly decreased after 2 h and external glucose concentrations were 3.5 ± 0.3 mmol/l after 26 h (Fig. 1). This corresponds to an overall 71% decrease in total glucose diffusion compared to control ($p < 0.001$, Table 2). Similarly, avocado extract (50 g/l) decreased the overall glucose movement by 60% ($p < 0.001$ compared to control, Table 2) a mean external glucose concentration of 4.6 ± 0.4 mmol/l after 26 h ($p < 0.001$ compared to control, Fig. 1).

Extracts of coriander, eucalyptus, lucerne, mistletoe and mushroom (50 g/l) significantly decreased glucose diffusion compared to control ($p < 0.001$, Fig. 2) with mean external glucose concentrations at 26 h ranging from 6.4 ± 0.2 mmol/l (coriander) to 7.8 ± 0.3 mmol/l (lucerne). However, the two most effective plant extracts of this group (coriander and eucalyptus) were 32–37% less effective at inhibition of glucose movement than agrimony extract. Table 2 illustrates the effects of these plants on glucose diffusion out of the dialysis tube (indicated by AUC for concentration of glucose in the external solution over time) and demonstrates differences in decreasing glucose movement over the test period from 48% (eucalyptus) to 25% (lucerne) (all $p < 0.01$ compared to control, Table 2).

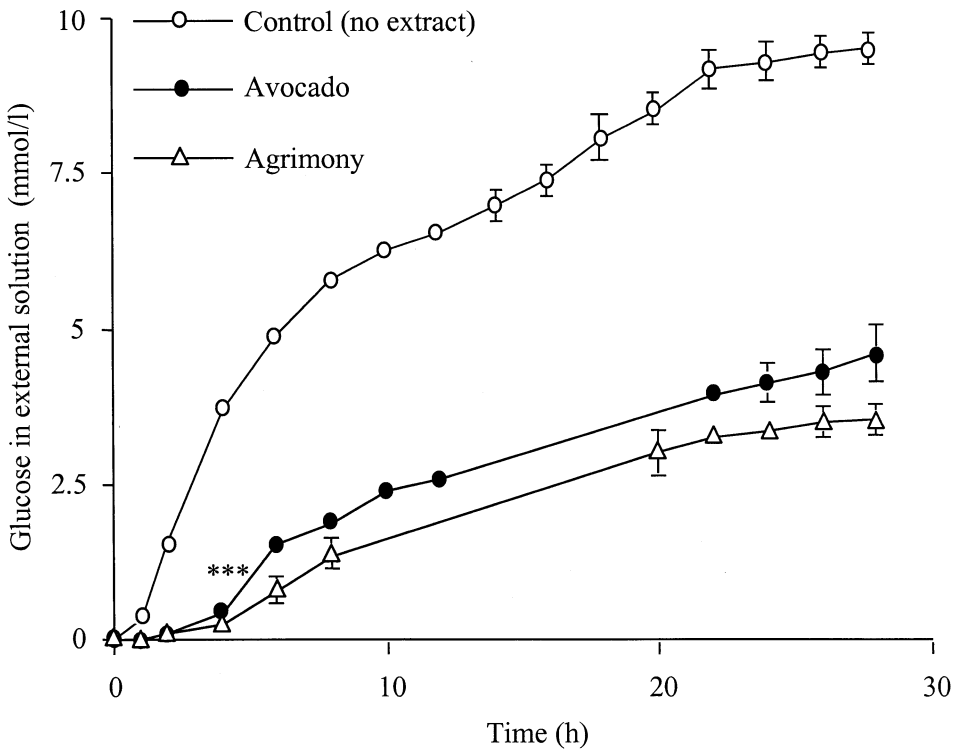

Fig. 1. Effect of 50 g/l aqueous extract of agrimony and avocado on the movement of glucose diffusion out of dialysis tube. Values are means ± SEM for groups of 3 observations with their standard errors indicated by vertical bars. ***$p < 0.001$ for both plants compared with control at this time and all subsequent times.

Glucose movement out of dialysis tube was unaltered by the presence of aqueous extracts of elder and nettle (50 g/l, Fig. 3). For these plants, the overall rates of glucose movement into external solution were similar to control. Juniper decreased decreased glucose movement by 6% (Table 2).

Concentrations of glucose concentrations inside the dialysis tubing after 26 h incubation in the absence or presence of plants were inversely related to the glucose concentrations in the external solution. Agrimony and avocado increased glucose concentrations inside the tube compared to control (53.4 ± 1.91 and 45.3 ± 2.13 versus 9.7 ± 0.60 mmol/l respectively; $p < 0.001$). Similarly, coriander, eucalyptus, mistletoe, and mushroom extracts decreased glucose concentrations in the tube when compared to control (27.9 ± 3.40, 39.2 ± 4.20, 22.2 ± 1.68, 24.4 ± 1.09, and 19.9 ± 2.65 versus 9.7 ± 0.60 mmol/l respectively; $p < 0.01$). The presence of elder, juniper and nettle extracts did not alter glucose concentrations in the tube from control levels (9.9 ± 1.47, 11.8 ± 2.75 and 10.4 ± 1.73 versus 9.7 ± 0.60 mmol/l respectively).

3.2. Concentration-dependent studies of effect of plant extracts on glucose diffusion

Different concentrations of agrimony, avocado, coriander and mushroom extracts were used to investigate their dose-dependent on glucose diffusion. The plant extracts exhibit a

Table 2
Effect of aqueous plant extracts (50 g/l) on the movement of glucose out of dialysis tube over 26 h incubation period

Test	Glucose in external solution	
	AUC[1] (mmol/l per 26 h) Mean ± SEM	Decrease of movement[2] %
Control:		
In absence of extract	164.8 ± 0.61	
Plant extract (50 g/l)		
Agrimony	47.3 ± 6.63	71%***
Avocado	65.7 ± 2.18	60%***
Coriander	91.4 ± 3.49	45%***
Elder	163.4 ± 0.81	—
Eucalyptus	85.4 ± 11.35	48%***
Juniper	155.5 ± 1.03	6%**
Lucerne	123.6 ± 2.82	25%***
Mistletoe	112.4 ± 1.73	32%***
Mushroom	120.0 ± 6.79	27%***
Nettle	158.1 ± 5.37	—

Values are means (SEM) for groups of 3 observations.
**$p < 0.01$,
***$p < 0.001$ compared to control.
[1] AUC (area under the curve) was calculated according to Burington [24] using total glucose diffusion over 26 h incubation period as described in the methods section and expressed as mmol/l per 26 h.
[2] Percentage decrease in movement of glucose into the external solution in comparison to control.

concentration-dependent inhibitory effect on glucose movement (Fig. 4). Agrimony inhibited glucose diffusion at each tested concentration (6.25, 12.5, 25 and 50 g/l) of extract (Fig. 4a, $p < 0.001$). The external glucose concentrations after 26 h were greater at 6.25 g/l compared to 50 g/l (8.3 ± 0.36 versus 3.6 ± 0.2 mmol/l respectively, $p < 0.001$). A similar concentration-dependent decrease in glucose movement was observed with avocado (Fig. 4b). Extracts of coriander and mushroom also inhibited significantly glucose movement except at the lowest concentration (6.25 g/l) (Fig. 4c–d).

4. Discussion

Over 400 plants have been documented as being useful for control of blood glucose concentration; however, the majority of these plants have yet to be scientifically or medically evaluated [10]. Dietary control of diabetes is fundamental to the management and treatment of NIDDM. In the last few decades, a number of studies have indicated the value of plant fibre or complex carbohydrates, including highly viscous soluble fibres such as guar gum and (β-glucan, for control of blood glucose concentrations [7–8,25–27]. Most of these plant components are highly unpalatable and are rarely included into the diet of type 2 diabetic subjects [9].

In the present study, a simple *in vitro* dialysis-based model was used to investigate how

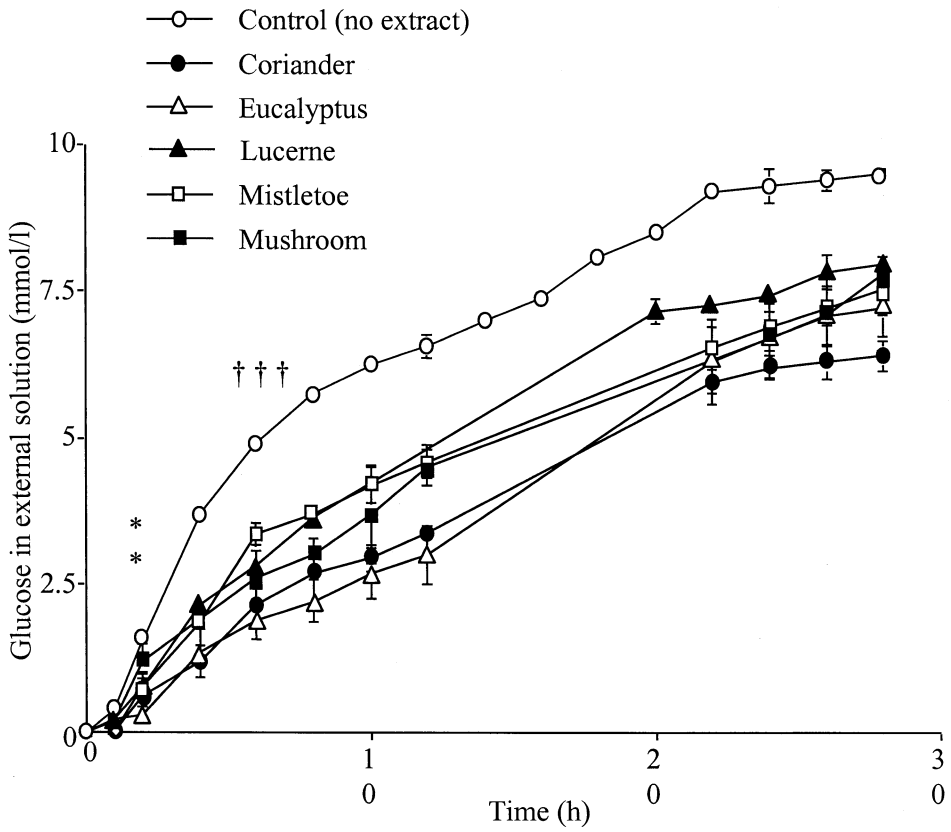

Fig. 2. Effect of 50 g/l aqueous extract of coriander, eucalyptus, lucerne, mistletoe and mushroom on the movement of glucose out of dialysis tube. Values are means ± SEM for groups of 3 observations with their standard errors indicated by vertical bars. $^{**}p < 0.01$ for eucalyptus compared with control at this time and all subsequent times. $\dagger\dagger\dagger p < 0.001$ for coriander, lucerne, mistletoe and mushroom compared with control at this time and all subsequent times.

various aqueous plant extracts that exhibit antidiabetic properties as dietary supplements [3,15,28] affect glucose diffusion. With the exception of nettle and avocado, the antihyperglycemic activity of these plants *in vivo* was associated with the ability of soluble components to increase glucose uptake and metabolism in muscle or to stimulate insulin secretion (Table 1). Decreasing gastrointestinal glucose convection and diffusion is now thought to be the reason why viscous plant components have antihyperglycemic properties [9]. Whilst the model system employed constant agitation to mimic gastrointestinal convection, the model may be limited in that the time for glucose to completely diffuse from the dialysis tube (22–26 h) is not directly comparable with the timing of cellular mechanisms of glucose absorption within the gut. However guar, a known inhibitor of intestinal glucose absorption substantially reduces glucose diffusion in this model system (data not shown) illustrating that it mimics the *in vivo* effect at least in part.

Aqueous extracts of agrimony and avocado demonstrated significant concentration-dependent inhibitory effects on glucose movement into external solution across dialysis

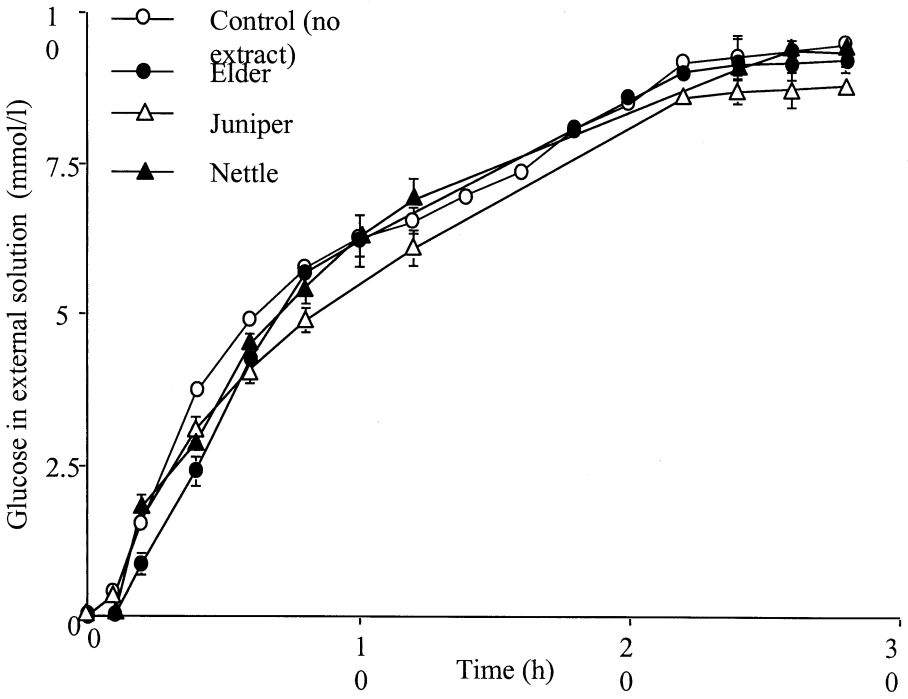

Fig. 3. Effect of 50 g/l aqueous extract of elder, juniper and nettle on the movement of glucose diffusion out of dialysis tube. Values are means ± SEM for groups of 3 observations with their standard errors indicated by vertical bars. There were no significant differences compared with control incubations.

membrane. Recent research has shown that agrimony incorporated into the diet and drinking water decreases the weight loss, polydipsia, hyperphagia and hyperglycaemia of STZ-treated diabetic mice [14,18]. Aqueous extracts of agrimony increased pancreatic insulin secretion and insulin independent glucose uptake and metabolism *in vitro* [18]. The antihyperglycemic activity of avocado has been documented in humans using controlled dietary experiments [28]. Partial replacement of complex carbohydrates in the diet of type 2 diabetic subjects with avocado extracts significantly improved plasma lipid and glucose concentrations [27]. An additional benefit of avocado is that it is an excellent source of monounsaturated fatty acids [29].

In increasing order, aqueous extracts of mushroom, mistletoe, coriander, eucalyptus and lucerne exerted a significant inhibitory effect on glucose movement (25–48%) from dialysis tube to external solution. As shown in Table 1, previous studies have demonstrated that these plant extracts increased pancreatic insulin secretion and insulin dependent glucose uptake and metabolism *in vitro* [16–17,19–21]. The effects on glucose convection and diffusion were approximately 50% of those exerted by agrimony and avocado.

Aqueous extracts of elder and nettle did not influence glucose diffusion whereas a small 6% decrease was observed with juniper. Recent studies demonstrated that elder extract *in vitro* increased pancreatic insulin secretion and insulin dependent glucose uptake and metabolism [22]. Given the lack of effect of elder in the present study, the antidiabetic actions

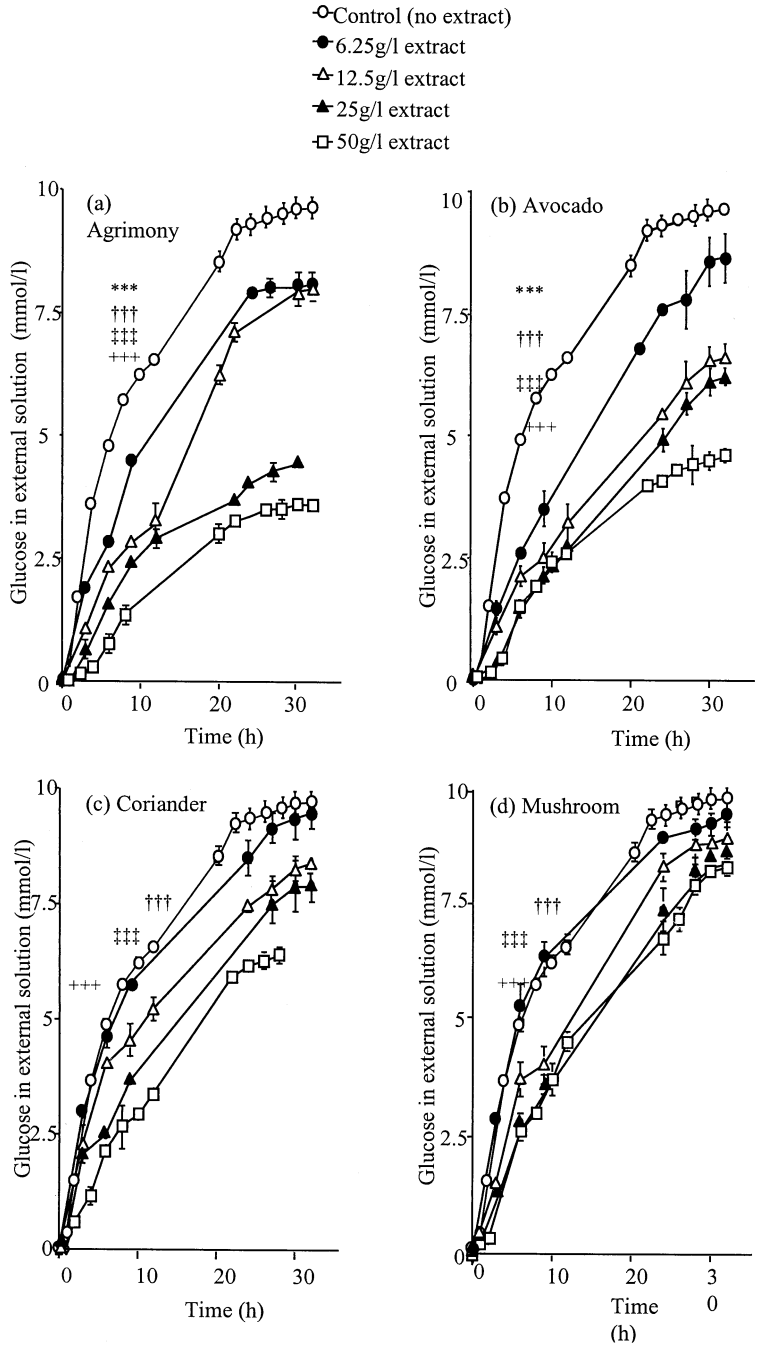

Fig. 4. Dose-dependent effects of aqueous extracts of (a) agrimony, (b) avocado, (c) coriander, and (d) mushroom on the movement of glucose out of dialysis tube. Values are means ± SEM for groups of 3 observations with their standard errors indicated by vertical bars. ***$p < 0.001$ for 6.25 g/l, †††$p < 0.001$ for 12.5 g/l, ‡‡‡$p < 0.001$ for 25 g/l and +++$p < 0.001$ for 50 g/l extract compared with control at this time and all subsequent times.

of elder are not likely to be related to intestinal absorption. Previous studies demonstrated that juniper could aggravate the polydipsia and hyperglycemia in STZ-treated mice [3]. Additionally, juniper extract increased *in vitro* insulin secretion by decreasing cell viability [3]. In earlier studies, nettle did not alter glucose homeostasis in normal mice but aggravated the diabetic condition of STZ-treated mice [13]. These findings taken together with the observed lack of effect of juniper and nettle on glucose absorption in the present study question the usefulness of these two plants as an antidiabetic remedy.

The potential mechanism by which the plant extracts (in particular agrimony and avocado) inhibit glucose movement was not investigated in the present study. Published research suggests that there is a direct relationship between a plant's ability to inhibit glucose absorption and the viscosity of the plant's constituent soluble polysaccharides [9]. The viscosity of plant extracts was not determined in the present study. Other investigators suggest that concentration and molecular mass of soluble fibres are major determinants of the plant's antihyperglycemic activity [27]. *In vivo*, plant fibres alter gastric emptying time, small intestinal transit time, and colonic emptying via different mechanisms [30]. By binding water, cations, and bile acids or by forming gels that sequester mono- or di-saccharides, fibre-containing foods modify both the digestive and absorptive processes. Although the effects of the several different types of fibres on these physiological processes are not known, it is apparent that the *in vivo* actions of fibres may differ from those *in vitro*. Osmolarity, pH, the mixture of fibres and nutrients, water retention, and the presence of bacteria influence the physiologic action of specific fibres [30].

In conclusion, the present study demonstrates the ability of various aqueous plant extracts to inhibit glucose diffusion using an *in vitro* model of glucose absorption. In particular, agrimony (*Agrimony eupatoria*) and avocado (*Persea americana*) represent potential dietary supplements that may be useful for allowing flexibility in meal planning in type 2 diabetes. Further studies are required to elucidate whether *in vitro* effects represent therapeutic potential by limiting postprandial glucose absorptions and for improving glycemic control in type 2 diabetic subjects.

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