RESEARCH ARTICLE

Polyphenols and phenolic acids from strawberry and apple decrease glucose uptake and transport by human intestinal Caco-2 cells

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The effect of polyphenols, phenolic acids and tannins (PPTs) from strawberry and apple on uptake and apical to basolateral transport of glucose was investigated using Caco-2 intestinal cell monolayers. Substantial inhibition on both uptake and transport was observed by extracts from both strawberry and apple. Using sodium-containing (glucose transporters SGLT1 and GLUT2 both active) and sodium-free (only GLUT2 active) conditions, we show that the inhibition of GLUT2 was greater than that of SGLT1. The extracts were analyzed and some of the constituent PPTs were also tested. Quercetin-3-*O*-rhamnoside (IC_{50} = 31 μM), phloridzin (IC_{50} = 146 μM), and 5-caffeoylquinic acid (IC_{50} = 2570 μM) contributed 26, 52 and 12%, respectively, to the inhibitory activity of the apple extract, whereas pelargonidin-3-*O*-glucoside (IC_{50} = 802 μM) contributed 26% to the total inhibition by the strawberry extract. For the strawberry extract, the inhibition of transport was non-competitive based on kinetic analysis, whereas the inhibition of cellular uptake was a mixed-type inhibition, with changes in both V_{max} and apparent K_m. The results in this assay show that some PPTs inhibit glucose transport from the intestinal lumen into cells and also the GLUT2-facilitated exit on the basolateral side.

Keywords:
Apple / Caco-2 cell / Glucose transport / Polyphenols / Strawberry

1 Introduction

One of the major and consistent recommendations for health in many countries is to increase consumption of fruits and vegetables up to 5-(portions)-a-day (or more). Fruit juice consumption is increasing, and these products are sometimes included in the 5-a-day recommendation, although sugar content can be fairly high. Apples and strawberries form an important part of the fruit and juice consumption in many populations, and the fruits are high in flavonoids and phenolic acids. The compounds in strawberries are anthocyanins, flavonols, flavanols and derivatives of hydroxycinnamic and ellagic acids [1–3]. Apples contain flavanols, especially (−)-epicatechin and procyanidins, hydroxycinnamic acids (mainly 5-caffeoylquinic acid and 4-*p*-coumaroylquinic acid), dihydrochalcones, phloridzin (phloretin glucoside), phloretin xyloglucoside, flavonols and in some varieties anthocyanins (present only in peel) [4, 5].

Repeated high post-prandial plasma glucose ''spikes'' are associated with an increased risk of developing cardiovascular diseases, metabolic syndrome and type II diabetes [6, 7]. Unregulated glycemic excursions are undesirable, and any reduction or ''blunting'' of the post-prandial glucose concentration in blood is potentially beneficial. There is recent evidence that some bioactive compounds, in particular polyphenols, phenolic acids and tannins (PPTs), can

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Abbreviations: **IC_{50},** concentration estimated to give 50% inhibition; **PPT,** polyphenol, phenolic acid and tannin; **SGLT,** sodium-dependent glucose transporter

affect the shape of the blood glucose curve [8–10]. Some studies have shown that these compounds may result in an altered pattern of intestinal glucose uptake [8, 10–12], possibly due to interactions between compounds and enterocyte sugar transporters.

Glucose transport is of fundamental importance in energy metabolism, and hence, the transport of glucose across cell membranes plays a key role in metabolic regulation and control. In the intestine, glucose is transported mainly by two transporters, depending on the luminal glucose concentration. At low concentrations of glucose, glucose is transported against a concentration gradient by an active transport mechanism in which glucose is co-transported with sodium ions *via* the high affinity sodium-dependent glucose transporter 1 (SGLT1) ($K_m = 0.2$ mmol/L) [13]. At higher concentrations of glucose, it is mainly transported by the lower affinity facilitated transporter, GLUT2 ($K_m = 40$ mmol/L) [13]. GLUT2 is thought to be localized to the membrane only at higher concentrations of glucose, whereas SGLT1 is constitutive [14].

PPTs can interact with certain sugar transporters, for example, by competitive inhibition of SGLT1 [15, 16], or by inhibition of GLUT2 [10]. The inhibitory effects of flavonoids on cellular transport occurred at concentrations of around 100 μM [10, 17], which is easily reached and even surpassed in the intestinal lumen [18]. Therefore, PPTs have the potential to readily affect glucose absorption in the small intestine. We have tested the effects of some PPTs on the sugar transporters GLUT2 and SGLT1 in intestinal Caco-2 cells, which express high levels of both transporters [19]. The data indicate that the PPTs from strawberry and apple are potent inhibitors of GLUT2 and SGLT1 at concentrations predicted after dietary ingestion. Therefore, the consumption of strawberry and apple juices could affect glucose absorption *via* the inhibition of glucose transport.

2 Materials and methods

2.1 Standards and reagents

D-[U-^{14}C] glucose (50 μCi) was purchased from GE Healthcare (Buckinghamshire, UK). Pelargonidin-3-*O*-glucoside was purchased from Extrasynthese (Genay, France). Quercetin, phloridzin, 5-caffeoylquinic acid, *p*-coumaric acid, quercetin-3-*O*-rhamnoside, epicatechin, DMEM (4500 mg/L glucose) and the Bradford reagent were purchased from Sigma (Poole, UK). Caco-2 cells were obtained from the American Type Culture Collection (Middlesex, UK).

2.2 Cell cultures

Cells were cultured in a humidified CO_2 incubator (Sanyo, MCO-18AIC) in an atmosphere of 5% CO_2–95% air (v/v; O_2 partial pressure of 150 Torr) at 37°C. Caco-2 cells were grown in DMEM (4500 mg/L glucose), supplemented with 15% heat-inactivated fetal calf serum, 2% L-glutamine 200 mM, 1% non-essential amino acids, penicillin 100 U/mL and Amphotericin B 0.25 μg/mL. Caco-2 stock cell cultures were maintained in 75-cm^2 plastic dishes. The cells were sub-cultured at confluence by trypsin treatment before use in the experiments. Caco-2 cells for transport experiments were seeded and grown to confluence in 6-well plates (Corning® Transwell® polycarbonate membrane, pore size 0.4 μm, 24 mm diameter). All experiments were carried out on cells of passage number from 35 to 52.

2.3 Glucose transport measurements in Caco-2 cells

Caco-2 cells for transport experiments were seeded at 0.27 million cells/well; the medium was changed every 2 days and the experiment was carried out within 23 days. Differentiation of the monolayer was assessed by electrical resistance of the cell monolayers. Only Transwell inserts with a resistance exceeding a blank membrane by 300 Ω were utilized in the experiments. For experiments, medium was discarded and cells were washed twice with 2 mL of HEPES buffer solution A (HEPES, 20 mM; NaCl, 137 mM; KCl, 4,7 mM; $MgSO_4$, 1.2 mM; $CaCl_2$, 1.8 mM) in both upper and lower compartments (pH 7.4). After washing, 1 mL of HEPES buffer containing D-[U-^{14}C] glucose 0.5 μCi/mL and 1 mM total glucose (solution B), with or without PPTs or extract, was added to the upper compartment. Cells were then incubated for 30 min at 37°C, the electrical resistance measured, and buffer from the upper and lower compartments removed. Glucose uptake was stopped by washing each membrane twice with ice-cold PBS. After that, 1 mL of NaOH solution (0.1 mol/L) was added to lyse the cells, and aliquots were removed for scintillation counting and protein measurement. Glucose transport values were corrected for protein content, as determined by the Bradford method [20]. Scintillation solution (5 mL, Ecoscint XR scintillation solution, National Diagnostics) and 0.5 mL of the different test solutions were mixed and analyzed by scintillation counting using a Packard Liquid Scintillation Analyzer 1600TR. An untreated solution of 0.5 mL of HEPES buffer solution B was used to quantify the D-[U-^{14}C] glucose. K_m and V_{max} values were calculated from Lineweaver–Burk plots.

2.4 Sample preparation

The strawberries (var. Albion) and apples (var. golden delicious) were purchased from a local market (Leeds, UK). The strawberries and apples were blended (whole pieces without the stem/core) with a juice extractor (Philips, HR1851). The juice was centrifuged (5000 × *g* at 4°C) and the supernatant was stored at −20°C until analysis. The total solid content was 164 and 136 mg/mL in apple and strawberry extracts, respectively. Samples to test in cell culture experiments were

pre-treated as follows: 3 mL of each supernatant was passed through an SPE cartridge (Oasis, Waters, HLB 3 cc, 60 mg). The samples were then washed with 5 mL of H_2O to remove endogenous fruit sugars and a fraction (PPT-rich) was eluted with 5 mL of methanol. These solutions were concentrated by centrifugal vacuum evaporation to dryness, and portions dissolved in 1, 1.2, 1.5, 2 or 3 mL of solution B. Results are expressed in mg of solid/mL of transport solution. Pure compounds (pelargonidin-3-*O*-glucoside, phloridzin, 5-caffeoylquinic acid, *p*-coumaric acid, quercetin-3-*O*-rhamnoside and (−)-epicatechin) were dissolved in solution B.

2.5 HPLC-DAD-MS analyses

Analyses of apple and strawberry extracts were performed by reversed-phase LC followed by DAD and positive ion electrospray ionization with MS/MS. LC was performed with an Agilent (Palo Alto, CA, USA) 1200 Series LC system, which consists of a binary pump, vacuum degasser, autosampler, a thermostated column compartment and a diode array detector. MS detection was performed using an Agilent 6410 triple quadrupole LC/MS instrument. The data were processed using MassHunter Workstation Software from Agilent for qualitative analysis. The gas flow was nitrogen at flow rate of 6 L/min, capillary voltage was 4000 V, nebulization pressure 60 psi and the gas temperature was 300°C. Spectra were recorded in positive ion mode between *m/z* 150 and 2000. An Agilent XDB-C_{18}, 1.8 μm (4.6 × 50 mm) column, thermostated at 30°C, was used. The solvents were (A) 1% formic acid in water and (B) ACN. The elution gradient was 5–10% B in A over 5 min, 10–40% B in A over 15 min and 40–90% B in A over 5 min using a flow rate of 0.5 mL/min. The absorbance was recorded at 280, 310, 370, 450 and 520 nm. Hesperetin at 0.1 mM was used as internal standard. The PPTs of the strawberry and apple extracts were quantified against known standards where available, or against comparable compounds (Section 3).

2.6 Statistical analysis

Data are expressed as the mean ± standard deviation ($n = 3$). The mean values were from data obtained from three different six-well plates. Statistical analysis was performed by one-way analysis of variance using the software package SPSS (version 13.0; SPSS, Chicago, IL, USA). Significant differences were assessed with the least squares difference test ($p < 0.05$).

3 Results

3.1 Inhibition of glucose transport by extracts from strawberry and apple under sodium-dependent conditions in Caco-2 cells

In the presence of Na^+, Caco-2 cells take up D-[U-^{14}C]-glucose (1 mM) from the cell culture medium at a rate of ~0.75 nmol/min mg cellular protein and transport it to the basolateral side at ~6.5 nmol/min mL culture medium. Addition of extracts from strawberry or apple to the apical side led to a dose-dependent inhibition of both uptake and basolateral transport of D-[U-^{14}C]-glucose (Fig. 1A and B). The concentration required for 50% inhibition (IC_{50}) was calculated for both uptake of D-[U-^{14}C]-glucose into the cells and transport to the basolateral side (Table 1). These IC_{50} values show a substantial capacity of the extracts from strawberry and apple to inhibit glucose uptake and

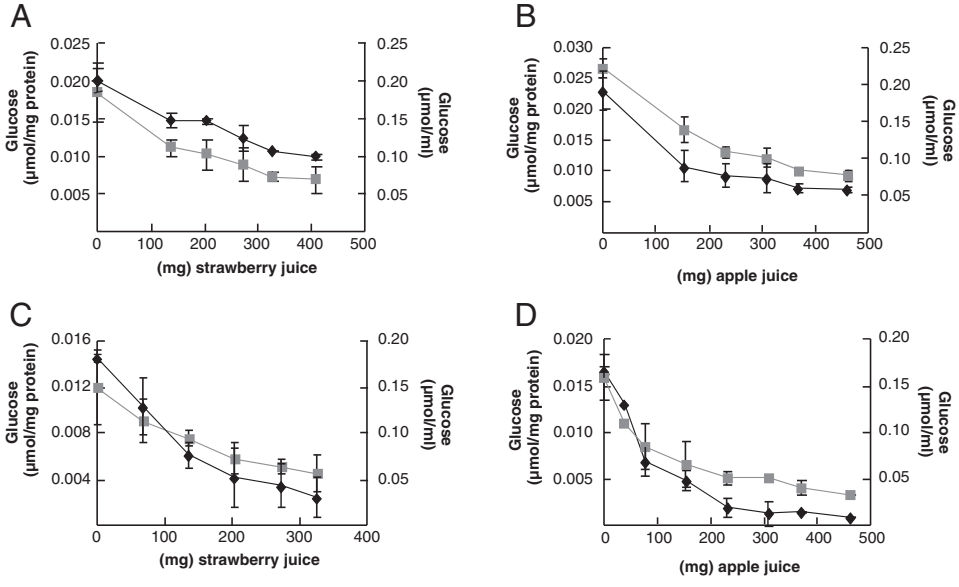

Figure 1. Effect of strawberry extracts (graphs A and C) and apple extracts (graphs B and D) on intracellular glucose concentration (grey square) and in the basal compartment (black triangle). The glucose transport was measured in Caco-2 cells treated under sodium-containing (graphs A and B) and sodium-free conditions (graphs C and D) with 1 mM glucose, D-[U-^{14}C] glucose 0.5 μCi/mL and strawberry extract. Each value is mean ± SE ($n = 3$).

transport. Under these conditions, it is expected that both SGLT1 and GLUT2 will operate at the apical surface, and GLUT2 at the basolateral side.

3.2 Inhibition of glucose transport by extracts from strawberry and apple extracts under sodium-free conditions in Caco-2 cells

The experiments above were repeated under sodium-free conditions, with potassium chloride replacing sodium chloride. Under these conditions, it is expected that only GLUT2 will operate at the apical surface, with the action of GLUT2 at the basolateral side unaffected. The total uptake of D-[U-^{14}C]-glucose and transport to the basolateral side was decreased (Caco-2 cells take up D-[U-^{14}C]-glucose (1 mM) from the cell culture medium at ~0.46 nmol/min mg cellular protein and transport it to the basolateral side at ~5.6 nmol/min mL culture medium) compared with culture medium containing sodium (Fig. 1C and D). Extracts from strawberry and apple inhibited both the cellular uptake and basolateral transport of glucose under these conditions. The IC_{50} values were lower showing greater inhibition under sodium-free conditions (Table 1).

The IC_{50} values for extracts from strawberries and apples were not statistically significantly different for uptake into cells, but were approximately fivefold different for inhibition of transport of [^{14}C]-glucose to the basolateral side. This implies that compounds in the apple extract can cross the cell membrane and subsequently inhibit basal transport more effectively than the compounds in strawberry. The result of these assays show that GLUT2 is the primary apical surface target of the compounds from apple and strawberry, and the absence of sodium, which prevents activity of SGLT1, does not greatly affect the pattern of inhibition.

3.3 PPT composition in apple and strawberry extracts

Since both the apple and strawberry extracts inhibited glucose transport, we analyzed the PPT content of these extracts using HPLC. The compounds were identified by UV spectra and mass spectrometric molecular ions, and quantified by the use of calibration curves of the relevant standards. The profile of the different PPTs in the strawberry extract is shown in Fig. 2 and the quantification is indicated in Table 2. The anthocyanins are the most abundant PPT component; as expected, the main anthocyanin is pelargonidin-3-*O*-glucoside. The cinnamic acids are also well represented in this extract with different isomers of *p*-coumaroyl hexose (*i.e.* an unknown hexose sugar such as glucose) and ferulic acid hexose, as quantified using a standard curve of *p*-coumaric acid. Some flavanols are also present, quantified against a (−)-epicatechin standard, and the flavonols were quantified using a standard curve of quercetin. These PPT contents are as expected and the proportions are comparable to other reports [21].

Table 1. Effect of strawberry and apple extracts on glucose transport under sodium-dependent and sodium-free conditions in Caco-2 cells

	Strawberry IC_{50} (mg solid)	Apple IC_{50} (mg solid)
Sodium-dependent conditions		
Apical GLUT2 and SGLT1	$227 \pm 71^{a\alpha}$	$300 \pm 62^{a\alpha}$
Apical and basal GLUT2 and SGLT1	$324 \pm 54^{a\beta}$	$66 \pm 38^{b\alpha}$
Sodium-free conditions		
Apical GLUT2	$102 \pm 27^{b\alpha}$	$146 \pm 33^{c\alpha}$
Apical and basal GLUT2	$121 \pm 20^{b\beta}$	$52 \pm 25^{b\alpha}$

Values are mean ± SEM of three different assays. Means of same column followed by different Latin letters differ significantly; means of the same row followed by different Greek letters differ significantly (Tukey test at $p < 0.05$).

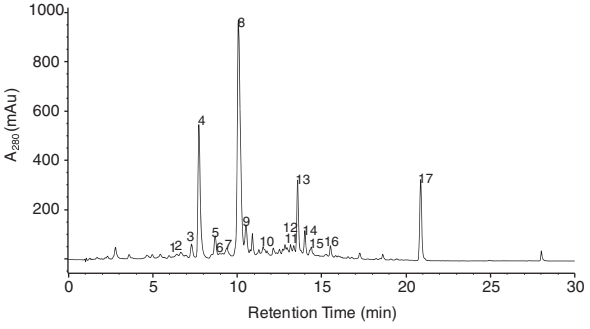

Figure 2. HPLC-DAD chromatogram of the strawberry extract recorded at 280 nm. For peak numbers, refer to Table 2.

The PPTs present in the extracts from apple are shown in Fig. 3 and quantified in Table 3. The content and amount of flavanols and cinnamates are as expected and consistent with the literature [4, 22]. As expected, phloridzin and phloretin-2-*O*-xyloglucoside, specific to apples, were present. Tannin fractions with a high degree of polymerization have been found in apple juice [4], but the analytical methods used here would not specifically identify these. As extracts containing these compounds inhibited glucose transport, we tested some of the major constituents as pure compounds for their ability to exhibit the same properties.

3.4 Glucose transport inhibition by pure PPTs in Caco-2 cells

The ability to inhibit [^{14}C]-glucose uptake and transport was tested with some compounds (10–500 μM), concentrations that are feasible in the small intestine after intake of these juices. Phloridzin, quercetin-3-*O*-rhamnoside and pelargonidin-3-*O*-glucoside were very effective inhibitors;

Table 2. Characterization of phenolic compounds in strawberry extracts using HPLC with DAD/MS with electrospray ionization

Peak number	Retention time, t_R (min)	Relative t_R to hesperetin	λ_{max} (nm)	Mass spectrometry (*m/z*)	Concentration (mM)	Compound
1	6.8	0.32	280	579	0.034	Dimer B1 (EC-4,8-C)
2	7.0	0.33	280	579	0.055	Dimer B3 (C-4,8-C)
3	7.5	0.35	280	291	0.091	(+)-Catechin
4	7.9	0.37	314	327	0.465	*p*-Coumaroylhexose
5	8.8	0.41	314	327	0.516	*p*-Coumaroylhexose
6	9.5	0.45	514	449	0.002	Cyanidin-3-*O*-glucoside
7	9.7	0.46	502	595	0.020	Pelargonidin-3-*O*-diglucoside
8	10.4	0.49	502	433	0.591	Pelargonidin-3-*O*-glucoside
9	10.9	0.51	502	579	0.063	Pelargonidin-3-*O*-rutinoside
10	11.1	0.52	338	451	0.040	Ferulic acid hexose
11	13.1	0.62	358	465	0.087	Quercetin-3-*O*-glucoside
12	13.5	0.63	358	479	0.084	Quercetin-3-*O*-glucuronide
13	13.8	0.65	284	328, 643		Unknown
14	14.3	0.67	284	328, 643		Unknown
15	14.6	0.69	348	449	0.096	Kaempferol-3-*O*-glucoside
16	14.8	0.69	348	463	0.079	Kaempferol-3-*O*-glucuronide
17	21.3	1.00	385	303		Hesperetin (IS)

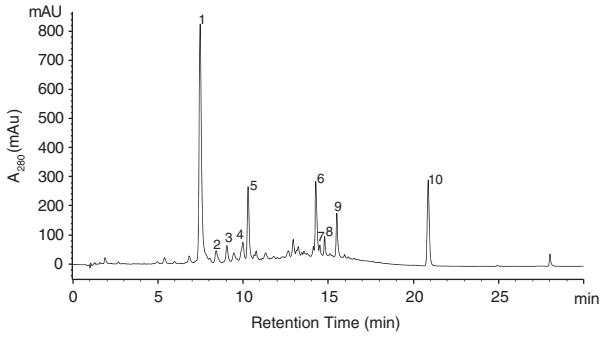

Figure 3. HPLC-DAD chromatogram of the apple extract recorded at 280 nm. For peak numbers, refer to Table 3.

5-caffeoylquinic acid and *p*-coumaric acid also demonstrated some inhibition. All of these compounds showed dose-dependent inhibition and, therefore, IC_{50} values could be calculated for both uptake and transport (Table 4). (−)-Epicatechin inhibition did not reach 50% even at 500 μM.

3.5 Determination of the kinetic mechanism of inhibition

To investigate inhibition by the extracts from strawberry further, the kinetics of the inhibition were measured. The V_{max} and apparent K_m values were measured for glucose uptake and transport between 0.5 and 40 mM glucose (Table 5 and Fig. 4). The catalytic efficiency (V_{max}/K_m) was similar for both processes, but the transport was faster (V_{max} higher) than uptake, although the uptake into cells showed a lower apparent K_m and lower V_{max}. Kinetic constants were measured at two different concentrations of strawberry extract for both uptake and transport. For transport of glucose to the basolateral side, the K_m for glucose was not significantly changed, whereas the strawberry extract reduced the V_{max}. This pattern is consistent with non-competitive inhibition. For uptake into cells, the V_{max} is reduced and the K_m is increased, which indicates a mixed-type inhibition.

4 Discussion

The results obtained demonstrate that PPT-rich extracts from strawberry and apple were able to influence glucose uptake into the cells and transport to the basolateral side by inhibiting activities of the glucose transporters. Some of the compounds can cross from the apical side into cells, and/or to the basolateral side, and consequently inhibit the GLUT2-facilitated glucose efflux on the basolateral side of the cells. Typical candidate metabolites, exported to the basolateral side, could be the deglycosylated, methylated, glucuronidated or sulfated derivative of the constituent flavonoids.

Some pure PPTs, constituents of strawberries and apples, were also tested. Analysis of the extracts for PPT content allowed estimation of the apparent contribution of the tested PPTs to the total inhibition catalyzed by the fruit extract. In the apple extract, the tested component PPTs contributed ~85% of the inhibitory activity. In the strawberry extract, only pelargonidin-3-*O*-glucoside (~26%) could be identified as a contributing inhibitor (Fig. 5). Possibly complex ellagitannins could contribute to some of this missing activity. These estimations, of course, assume no interactions between compounds.

The results with and without sodium suggest that the inhibition of GLUT2 (which is the dominant apical intestinal sugar transporter when intestinal glucose concentra-

Table 3. Characterization of phenolic compounds in apple extracts using HPLC with DAD/MS with electrospray ionization

Peak number	Retention time, t_R (min)	Relative t_R to hesperetin	λ_{max} (nm)	Mass spectrometry (m/z)	Concentration (mM)	Compound
1	7.4	0.48	326	355	0.331	5-Caffeoylquinic acid
2	8.3	0.53	326	355	0.029	3/4-Caffeoylquinic acid
3	8.8	0.57	280	579	0.052	Dimer B2 (EC-4,8-EC)
4	9.9	0.64	280	291	0.059	(−)-Epicatechin
5	10.2	0.66	312	339	0.085	*p*-Coumaroylquinic acid
6	14.1	0.91	284	569	0.054	Phloretin-2-*O*-xylo-glucoside
7	14.3	0.93	348	449	0.046	Kaempferol-*O*-glucoside
8	14.8	0.96	310	449	0.041	Quercetin-3-*O*-rhamnoside
9	15.5	1.00	284	437	0.031	Phloretin-2-*O*-glucoside
10	20.8	1.34	385	303		Hesperetin (IS)

Table 4. Inhibition of glucose transport by PPTs

Compound	Uptake into Caco-2 cells ($IC_{50\ (\mu M)}$)	Apical to basolateral transport ($IC_{50\ (\mu M)}$)
Pelargonidin-3-*O*-glucoside	705±78	802±102
Quercetin-3-*O*-rhamnoside	380±54	31±2
Phloretin-2-*O*-glucoside	468±116	146±32
(−)-Epicatechin	NI	NI
5-Caffeoylquinic acid	1269±130	2571±205
p-Coumaric acid	472±35	NI

NI = less than 50% inhibition at >500 μM.

Table 5. Kinetics of inhibition of glucose transport by strawberry extracts

	K_m (mM)	V_{max} (nmol/min)
Uptake[a]		
Control	1.5±0.09	3.5±0.5
Strawberry extract (136 mg)	2.6±0.60	2.6±0.5
Strawberry extract (272 mg)	4.2±0.44	2.2±0.2
Transport[b]		
Control	9±1.0	71±0.5
Strawberry extract (136 mg)	12±2.2	63±4
Strawberry extract (272 mg)	10±0.4	42±0.4

a) Transport into Caco-2 cells under sodium-containing conditions (apical SGLT1 and GLUT2).

b) Apical to basolateral transport across Caco-2 cells under sodium-containing conditions (apical SGLT1, apical and basal GLUT2).

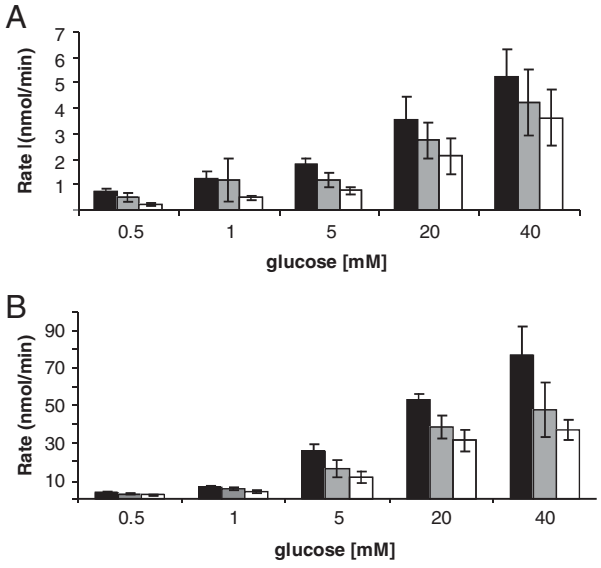

Figure 4. Rate of glucose transfer (A) from the apical side to inside the cells (uptake) and (B) from the apical to the basal side of Caco-2 cells. Black bars: controls cells without PPTs. Grey bars: cells treated with 136 mg/mL of strawberry extract. White bars: cells treated with 272 mg/mL of strawberry extract. Each value is mean±SE (n = 3).

tions are high) by extracts of both fruits is greater than inhibition of SGLT1 [23]. Data in the literature on the effect of PPTs on sugar transport across Caco-2 cells are very limited, although information exists for some related systems. Myricetin, fisetin and quercetin aglycones non-competitively inhibited glucose uptake into GLUT2-expressing *Xenopus* oocytes [10]. SGLT1 was competitively inhibited by galloylated green tea polyphenols as assessed using brush border membrane vesicles from rabbit small intestine. Tea polyphenols have been reported to inhibit SGLT1 competitively [11] or non-competitively [24]. (−)-Epigallocatechin gallate, (−)-epigallocatechin and (−)-epicatechin gallate inhibited both SGLT1 and GLUT2 and hence uptake of glucose (transport across the cells was not examined) into Caco-2 cells [12]. Under sodium-free conditions with only GLUT2 operating, quercetin, apigenin and myricetin, but not their glycosides, inhibited uptake into Caco-2 cells, whereas phloridzin, but not rutin or naringenin, inhibited SGLT1 under sodium-dependent conditions [12]. Using pig

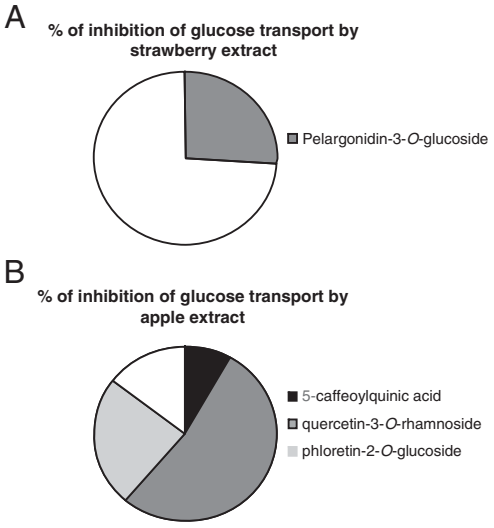

Figure 5. Percentage of inhibition by components of strawberry (A) and apple (B) extracts.

jejunal brush border membrane vesicles, quercetin-3-*O*-glucoside and quercetin-4′-*O*-glucoside inhibited glucose transport *via* inhibition of SGLT1, whereas rutin, quercetin-3-*O*-galactoside, quercetin aglycone, naringenin-7-*O*-glucoside, genistin and cyanidin-3,5-*O*-diglucoside were ineffective [16]. High concentrations of tannic acid (1 mg/mL) and of chlorogenic acid (1 mM) inhibited glucose transport using rat intestinal brush border membrane vesicles [24]. Phloridzin inhibits SGLT1 [12, 15] and also reduces the SGLT1 mediated re-absorption of glucose in several diabetic animal models [25, 26]. Procyanidins can lower glucose levels *in vivo* by delaying intestinal glucose absorption and by insulin-like effects on insulin-sensitive tissues [9]. A reduction in the glucose uptake due to the dissipation of the Na^+ electrochemical gradient may also lead to SGLT1 inhibition as proposed for tannic and chlorogenic acids [27]. Furthermore, intestinal SGLT1 gene expression is reduced in animals that received Yerba Mate [28]. Our study is the first to show inhibition of glucose transport across Caco-2 cells apical to basolaterally by PPT or fruit extracts, and to characterize the contribution of the phenolic component of those extracts to inhibition of glucose transport.

Inhibition of glucose uptake in the small intestine may prevent hyperglycemia, which is a risk factor for diabetes. Our results indicate that unsweetened beverages rich in these dietary PPTs might provide a dietary mechanism to dampen, blunt or regulate intestinal sugar absorption, a potentially important factor in the management of diabetes and the metabolic syndrome, and assist in the design of future intervention studies *in vivo*.

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