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REVIEW

# Possible effects of dietary polyphenols on sugar absorption and digestion

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Excessive post-prandial glucose excursions are a risk factor for developing diabetes, associated with impaired glucose tolerance. One way to limit the excursion is to inhibit the activity of digestive enzymes for glucose production and of the transporters responsible for glucose absorption. Flavonols, theaflavins, gallate esters, 5-caffeoylqunic acid and proanthocyanidins inhibit α-amylase activity. Anthocyanidins and catechin oxidation products, such as theaflavins and theasinsensins, inhibit maltase; sucrase is less strongly inhibited but anthocyanidins seem somewhat effective. Lactase is inhibited by green tea catechins. Once produced in the gut by digestion, glucose is absorbed by SGLT1 and GLUT2 transporters, inhibited by flavonols and flavonol glycosides, phlorizin and green tea catechins. These in vitro data are supported by oral glucose tolerance tests on animals, and by a limited number of human intervention studies on polyphenol-rich foods. Acarbose is a drug whose mechanism of action is only through inhibition of α-amylases and α-glucosidases, and in intervention studies gives a 6% reduction in diabetes risk over 3 years. A lifetime intake of dietary polyphenols, assuming the same mechanism, has therefore a comparable potential to reduce diabetes risk, but more in vivo studies are required to fully test the effect of modulating post-prandial blood glucose in humans.

**Keywords:**
Amylase / Diabetes / Disaccharide / Flavonoid / Glucose transport

A report almost 30 years ago indicated that total polyphenol content of foods was negatively correlated with glycemic index in both normal and diabetic volunteers [1] opening up an intriguing area for an effect of polyphenol action not related to their antioxidant or redox properties. Since then, many studies have been reported, and the effect of polyphenols on glucose homeostasis in human intervention studies was recently reviewed [2], concluding that despite some individually promising studies, the effects are not consistent. Epidemiological studies have supported the effect of polyphenol rich foods against the development of type II diabetes [3], such as coffee and tea [4, 5] and some herbal supplements [6], although the relationship to total fruits and vegetables intake and reduced diabetes risk is not so clear [7]. There is likely to be multiple mechanisms of action of polyphenols in reducing diabetes risk, and these have also been recently reviewed [3]; they include modification to post-prandial glycemic responses by inhibiting digestion or glucose transport [8], improved fasting blood glucose levels, enhanced insulin secretion and improved insulin sensitivity, mediated by stimulation of insulin from pancreatic β-cells, modification of hepatic glucose release, activation of insulin receptors and glucose uptake and modulation of signalling pathways and gene expression. This review will focus on the first step of the process, where the processes being affected are in the gut lumen. The gut lumen has, post-prandially, the highest concentration of polyphenols compared to any other site in the body by one or more orders of magnitude, and so is a prime likely target for effects on glucose metabolism. After consumption of beverages such as coffee, tea and orange juice, the concentration of polyphenols is likely to reach millimolar concentrations in the gut lumen (Table 1).

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**Abbreviations: IGT**, impaired glucose tolerance; **LPH**, lactase phlorizin hydrolase

## 1 Starch and di/monosaccharides in the diet

The main dietary sources of glucose are starch and various disaccharides, both of which must be digested before the component monosaccharides can be absorbed through the intestinal wall. Starch is a polysaccharide and consists of amylose and amylopectin, polymers of glucose linked by α-1,4

**Table 1.** Approximate concentrations of total polyphenols in various beverages and fruits using the Folin assay for total polyphenol measurement (from www.phenol-explorer.eu) [37]

| Beverage | Main constituent (poly)phenols | Approximate mean concentration of total polyphenols (Folin) in typical beverage or food (mg/100 mL or g), based on data from [37] | Very approximate and likely predicted total polyphenol concentration in the gut lumen (mM)[a)] |
|---|---|---|---|
| Filter coffee | Chlorogenic acids | 270 | 3 |
| Black tea | Thearubigins, flavanols, flavonols | 100 | 1.2 |
| Green tea | Flavanols, flavonols | 60 | 0.7 |
| Cocoa | Flavanols, procyanidins | 55[b)] | 0.6 |
| Orange juice | Flavanones | 50 | 0.6 |
| Apple juice | Flavanols, chlorogenic acids, dihydrochalcones, flavonols | 30 | 0.4 |
| Highbush blueberry | Anthocyanins, flavonols | 220 | 2.5 |
| Sweet cherry | Anthocyanins, flavanols, procyanidins, chlorogenic acids | 170 | 1.9 |

a) Concentration in the gut lumen calculated after addition of digestive juices assuming average molecular weight of polyphenols of 300 (the approximate molecular weight of a typical monomeric flavonoid; obviously oligomers will have a higher weight and hence lower molar concentration, with the opposite situation for phenolic acids), sole consumption and dilution by digestive secretions of threefold. These values are estimated and have not been measured in vivo; b) assuming 5 g cocoa powder in 100 mL liquid.

glycosidic bonds together with α-1,6-glycosidic bonds which form branch points mainly in amylopectin [9]. Starch is a major energy source in the diet and is broken down by a combination of enzymes to ultimately produce glucose, the absorbable 'unit'. When unhindered by other food components, amylose digestion occurs quite rapidly in the gut although this is dependent on the source and physical state of the starch [10].

Disaccharides such as sucrose and lactose in the diet are very common, and sucrose is the predominant sugar in most modern foods, together with lactose from dairy products. In some countries such as the USA, the monosaccharide sweetener fructose is very common in a wide range of food products. Sucrose and lactose are digested by enzymes to give glucose and one other sugar (fructose and galactose, respectively). Once produced in the gut lumen, glucose is efficiently absorbed through the gut wall and enters the bloodstream. This causes an increase in the blood glucose concentration, followed by release of insulin, which stimulates glucose uptake into other tissues. This glucose is then utilised or stored by those tissues and the blood concentration returns to baseline within 1–3 h. This increase in glucose concentration and subsequent decline is a critical hormone-dependent process, and has been subjected to intensive studies, since it plays a key role in the development of diabetes, and possible oxidative stress and ageing processes as well [11].

Glucose administered orally as a solution is rapidly absorbed in the small intestine and appears in blood. The area under the curve of the absorbed glucose in the blood is used as a reference value to which other foods are compared [12]. A glycemic index has been reported for many foods, where glucose = 100 and other foods are presented relative to this. In the absence of any inhibitory components, amylose has a glycemic index close to that of glucose, since it is rapidly digested. The presence of other components, including polyphenols, hinders this process, and so the area under the curve is decreased and the glycemic index is lower.

## 2 Digestion of carbohydrates into monosaccharides

α-Amylase (EC 3.2.1.1) hydrolyses the α-1,4-glycosidic bonds in both amylose and amylopectin, but cannot hydrolyse the α-1,6-glycosidic bonds which form the branch points. After hydrolysis of starch by α-amylase, the products are maltooligosaccaharides, consisting of two or more α-1,4-linked glucose units, together with limit dextrins, which contain uncleaved α-1,6-linked glucose units together with some remaining attached α-1,4-linked glucose units [9]. The reason for this product distribution is the specificity of α-amylase, an *endo*-acting enzyme, which means it acts 'randomly' on the starch chains and not at the end. The smallest product is maltose, i.e. at least 2 glucose units. α-Amylase is produced and secreted by salivary glands and by the pancreas, and the two enzyme isoforms have high sequence homology with similar but not identical specificities [13].

Sucrase and maltase hydrolyse disaccharides. Sucrose is glucose linked to fructose and is hydrolysed by sucrase (EC 3.2.1.48 – sucrose α-glucosidase) in the gut. This enzyme is isolated from intestinal mucosa as a single polypeptide chain that also hydrolyses isomaltose (EC 3.2.1.10

 

oligo-1,6-glucosidase) [14]. Maltose is a final product of starch digestion by α-amylase, and consists of 2 glucose units linked by an α-1,4 bond. It is hydrolysed by maltase/α-glucosidase EC 3.2.1.20 (also called maltase-glucoamylase). Human maltase-glucoamylase and sucrase-isomaltase are composed of duplicated catalytic domains displaying overlapping substrate specificities [15]. The N-terminal catalytic domain of human maltase has a preference for short linear α-1,4-oligosaccharides, whereas N-terminal sucrase-isomaltase has a broader specificity for both α-1,4- and α-1,6-oligosaccharides, hydrolysing linear α-1,4- and branched α-1,6-oligosaccharide substrates, the products of α-amylase action. Maltase-glucoamylase and sucrase-isomaltase are both attached to the brush border membrane of enterocytes via an O-glycosylated stalk stemming from the N-terminal domain and act on substrates in the gut lumen, although, unlike α-amylase, are not secreted [14]. The two enzymes both have α-glucosidase activity, which is the exohydrolysis of (1->4)-α-glucosidic linkages, with increased activity on smaller substrates and very little or no activity on polymers.

Lactose is found in milk and is the dominant sugar in this fluid. It consists of glucose linked to galactose by a β-1,4 linkage, and must be hydrolysed in the gut before absorption. Lactase EC 3.2.1.108, a brush border enzyme, hydrolyses β-1,4-glycosidic linkages such as those found in lactose. While several β-glucosidases are present in the small intestine, only lactase phlorizin hydrolase (LPH) is present on the luminal side of the brush border [16]. LPH has two active sites on the same polypeptide chain, one with high activity on lactose and the other on the plant-derived dihydrochalcone glucoside, phlorizin and on another component of milk, L-glycosylceramide (glycosylceramidase, EC 3.2.1.62; glucosylceramidase, EC 3.2.1.45; galactosylceramidase EC 3.2.1.46). LPH hydrolyses lactose from milk during infant years, is genetically regulated and declines during adolescence [17]. The majority of the population in the world have low levels of lactase as adults resulting in lactose maldigestion. However, populations with a history of consuming dairy produce, such as the Northern Europeans, retain LPH as adults [17].

## 3 Absorption of monosaccharides involves transporters

Once fully digested, glucose is the main product from dietary starch and disaccharides. As it is very hydrophilic and cannot cross biological membranes unaided, it is absorbed and moved around the body between tissues by transporters, predominantly comprising the families GLUTs and SGLTs [18]. These function by moving glucose from one compartment to another across a biological membrane, in particular from outside the cell to inside, or vice versa. Glucose transporters are regulated at the transcriptional level, but also by intracellular translocation where the transporter moves from a location in which it is inactive to another location where it is active, such as the regulation of GLUT4 by insulin. In the presence of insulin, GLUT4 is relocated from storage vesicles to the surface of adipocytes, effectively an activation of the transporter [19]. The main transporters for glucose in the small intestine are SGLT1 and GLUT2. These also function for galactose, but the main transporter for fructose is GLUT5. SGLT1 is a classical $Na^+$/glucose co-transporter, which is permanently located in the brush border membrane at the apical side of enterocytes. This active transporter is a member of the SLC5 gene family [20]. The $K_m$ of SGLT1 for glucose and galactose is 0.5 mM with two $Na^+$ transported for each glucose molecule [20]. Phlorizin is a classical inhibitor of SGLT1 with $K_i \sim 200$ nM. GLUT2 is a facilitative transporter, which is responsible for glucose absorption in the gut especially at high glucose concentrations. Originally this proportion of the absorption was thought to be paracellular, but it was later revealed that it is mediated by the GLUT2 transporter, which is rapidly moved to the apical membrane within a few minutes in the presence of high glucose concentrations [21]. As the glucose concentration decreases, as a result of absorption or at the end of the meal, the GLUT2 transporter moves away from the apical membrane ready for the next incidence of high glucose. Experimental diabetes can lead to GLUT2 permanently located at the apical membrane, resulting in increased and unregulated glucose absorption, characteristic of the insulin resistant state [21] (Fig. 1). Artificial sweeteners such as acesulfame and sucralose also stimulate translocation of GLUT2 to the apical membrane [22]. The passage and digestion of nutrients into the small intestine stimulates incretin hormone release, a critical factor in regulating the glycemic response. The key hormones, released from enteroendocrine cells in the intestinal epithelium, are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1. Glucose transporters such as SGLT1 play a role in regulating this response [23].

Once glucose is absorbed into the blood from the intestine, it enters β-cells via GLUT2 transport and subsequent phosphorylation of glucose ultimately stimulates insulin secretion. Insulin reaches muscle and adipose cells, causes GLUT4 relocation to the cell membrane and so facilitates glucose uptake into these tissues and consequent clearance from the blood.

## 4 Oral glucose tolerance test and fasting glucose

Glucose metabolism and regulation constitute key metabolic processes, and dysregulation or malfunctioning leads to serious illnesses such as type II diabetes. Normally post-prandial glucose is cleared rapidly from the blood, and efficiency of this is assessed using an oral glucose tolerance test [24, 25]. In the metabolic syndrome, impaired glucose tolerance (IGT) is linked to a high risk of developing diabetes. Excessive post-prandial glucose excursions in IGT and in type II diabetes are also associated with a cascade of pro-atherogenic events. Post-prandial hyperglycaemia is one of the earliest indicators of

 

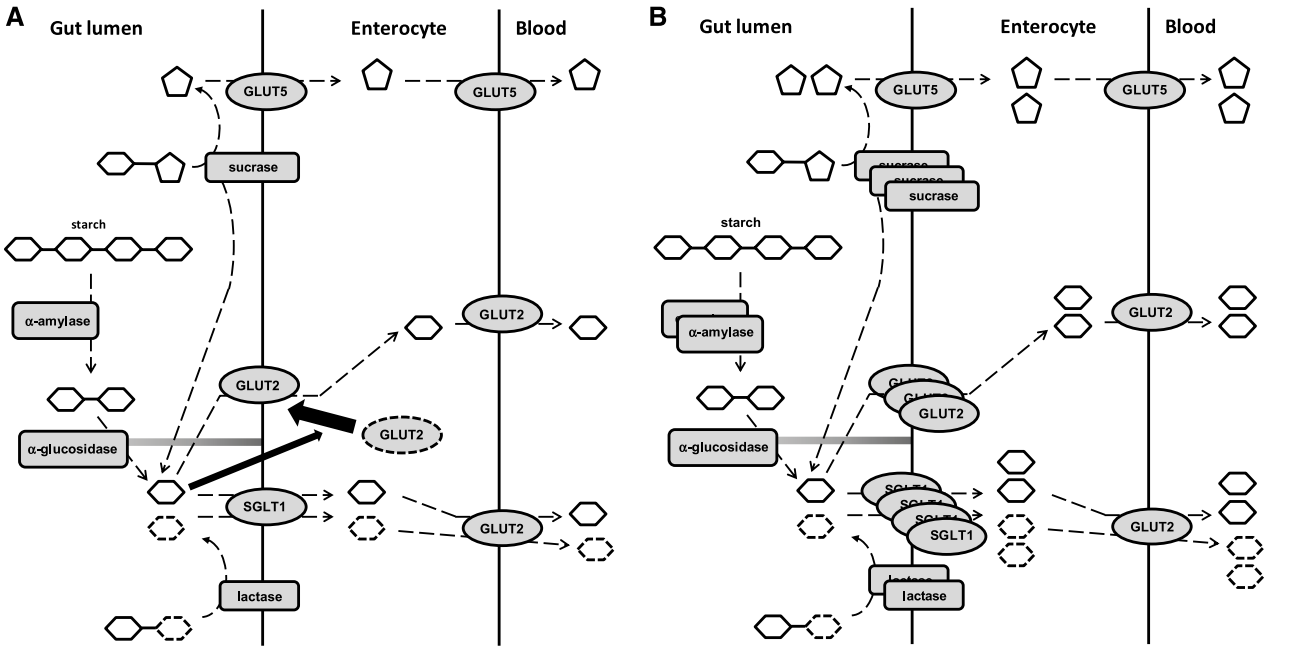


**Figure 1.** Diagrammatic representation of glucose absorption in the small intestine. Broken arrows show enzyme or transporter-mediated reactions, which are potential targets for polyphenols. Solid black arrows show regulatory pathways. (A) The situation in normal healthy individuals, and (B) the situation in diabetic patients where the levels of many sugar metabolising enzymes and transporters are upregulated, leading to enhanced post-prandial glucose absorption into the blood and impaired glucose tolerance in an oral glucose tolerance test. The six membered ring represents glucose, the five membered ring represents fructose and the six membered ring with broken line represents galactose.

impaired glucose control and an important strategy for managing diabetes risk is to lower post-prandial blood glucose levels. In diabetes, many of the enzymes and transporters responsible for sugar uptake in the gut are upregulated (Fig. 1B). SGLT1 protein levels are increased up to fourfold in the duodenum of type II diabetics, and mRNA of brush border enzymes such as sucrase and lactase are increased two- to threefold. GLUT2 mRNA is also increased threefold [26]. Brush border membrane vesicles from duodenal biopsies from diabetic patients take up glucose approximately threefold faster than the equivalent from control subjects [26]. Administration of hypoglycaemic drugs such as sulfonylureas and biguanides did not affect the expression levels in diabetic patients, but augmented insulin secretion, suggesting that the enhanced expression in diabetes is independent of blood glucose or insulin levels [26]. α-Amylase is also higher in diabetics [27]. All of these factors will contribute to an IGT condition, which exacerbates the poor glucose control in diabetes. The absorption of glucose from the gut, however, may be less affected than immediately apparent from the intestinal expression data described above. This is because the insulin-induced stimulation of splanchnic glucose uptake is impaired in type II diabetes [28].

Diabetes is characterised by a permanent substantial increase in fasting glucose, and in metabolic syndrome, the fasting glucose levels are also elevated. These changes are associated with increased glycation and oxidative stress leading to impaired glucose regulation with multiple further complications and problems [29]. Glucose regulation is related to changes in weight according to a systematic review of 22 studies, although the relationship is complex [30]. Higher serum glucose levels are even associated with a higher perceived age in non-diabetic individuals [31].

## 5 Polyphenols in the diet

Polyphenols are present in most foods which contain, or are derived from, plants, including fruits, vegetables, cocoa, coffee, tea and fruit beverages, and almost any foods containing parts or extracts of plants. There are various classes of polyphenols, and the most common in the diet are anthocyanins, flavanols (including catechins, proanthocyanidins, thearubigins and tannins), flavonols, phenolic acids, isoflavones, ellagitannins, flavones and flavanones. These have been the subject of numerous reviews summarising the structures and content [32–36] while the polyphenol content of some foods can be found in databases [37]. Many polyphenols are found in foods in the conjugated form, covalently linked to sugars, by O-glycosidic or less commonly by C-glycosidic bonds, and to organic acids, by ester bonds such as in chlorogenic acids and in green tea catechins. In beverages such as coffee, tea, cocoa and fruits juices, polyphenols can easily reach millimolar concentration, and this can

 

persist into the small intestine even when accounting for some dilution with other foods and digestive fluids. Once in the small intestine, enzymes such as LPH act on the β-glucosidic linkages to release free aglycones as shown for quercetin from quercetin glucosides, e.g. [38]. Thus, the milieu of the small intestinal lumen can contain a mixture of polyphenols stemming from the food together with aglycone forms from enzyme action, all of which can interact with secreted digestive enzymes, with membrane-bound brush border enzymes and with intestinal apically located transporters (Fig. 1). Any potential interaction can be influenced by the presence of other components derived from saliva, stomach and pancreatic secretions, and from the bile.

## 6 Human intervention studies and animal models to support the effect of polyphenols on glucose metabolism and diabetes risk

Many intervention studies have examined the effect of polyphenol-rich foods on post-prandial blood glucose levels in volunteers. A reduction in apparent glycemic index was seen for red wine, sugar cane extract, coffee, berries and apple juice (reviewed in [3]). Procyanidin-rich chocolate prevented the unfavourable glucose response induced by the control polyphenol-free chocolate in a crossover study in volunteers, when fed for 4 weeks [39]. A systematic review of herbs and dietary supplements for glycemic control was mostly inconclusive, but American ginseng and *Coccinia indica* were promising [40]. Another systematic review showed that supplementation with *Ipomoea batatas*, *Silybum marianum* and *Trigonella foenum-graecum*, but not *Cinnamomum cassia*, may improve glycemic control in type II diabetes [6].

Some animal studies have shown a similar effect, and compounds that inhibited glucosidases were effective at reducing post-prandial blood glucose levels. An extract of *Cassia auriculata* (Ranawara, a Sri Lankan herb), which inhibited maltase, but not sucrase, decreased glucose in blood when administered with maltose, but did not lower blood glucose when given with sucrose or glucose [41]. 6-*O*-caffeoylsophorose and theaflavin-3-*O*-gallate inhibited maltase in vitro and decreased post-prandial blood glucose when given with maltose to rats [42, 43]. Tiliroside (kaempferol 3-*O*-(6″-*O*-*p*-coumaroyl)-β-D-glucoside) inhibited α-amylase, SGLT1 and GLUT2, and inhibited the increase in post-prandial blood glucose after starch administration to male mice [44]. Naringenin, but not the glycoside naringin, inhibited glucose uptake in the intestine as assessed using brush border membrane vesicles in vitro, and also demonstrated an antihyperglycemic action in vivo [45]. Cocoa proanthocyanidins prevented the increase of blood glucose in genetically diabetic obese mice, with no effects on body weight or total food consumption [46]. Naringin also exhibited a comparable effect when fed in a similar model [47]. In streptozocin-induced diabetic rats, procyanidins showed an antihyperglycemic effect and procyanidins were even proposed to have an insulin-like effect [48]. Luteolin weakly inhibited maltase activity with $IC_{50}$ of 2.3 mM, compared to 430 nM for acarbose. After oral administration of acarbose, the blood glucose levels were significantly lower after 30 min compared to control, but luteolin had no effect [49] probably owing to the weak effect of luteolin on maltase compared to acarbose.

## 7 Models used to study the effect of polyphenols on the different steps of sugar digestion and absorption

In vitro assays to measure enzyme inhibition are relatively straightforward to perform. Ideally, a human enzyme is used, with the real substrate at physiological concentrations, and the assay is carried out simulating gut lumen conditions. However, this is rarely achieved. Many studies use porcine enzymes, which have a reasonable match to human sources, but other studies use a yeast enzyme, which has very different specificities to human or porcine enzymes [50, 51].

Hydrolysis of the actual substrate, such as maltose or sucrose, requires estimation of at least one of the released sugars. The glucose produced is usually measured using glucose oxidase or hexokinase, where the enzyme action is coupled to a suitable chromophore measured in a spectrophotometer. One problem to overcome is that many polyphenols inhibit the enzymes used to estimate glucose, and so an intermediate step is introduced to remove the polyphenols before glucose estimation. Occasionally, the glucose is measured by HPLC, which is the best method but also the most expensive and time-consuming. Easy to use alternative substrates exist, consisting of sugars linked to a *p*-nitrophenyl group; upon hydrolysis, the easily measured yellow nitrophenol anion is released. However, these are less specific than the physiological substrate and the affinity for the enzyme is less than the affinity for the real substrate. The presence of other proteins in the digestive mix, especially salivary proline-rich proteins, will also influence the inhibition but this effect is usually ignored.

α-Amylase is commonly assayed using starch as substrate with detection of reducing sugars, or using synthetic substrates such as blocked *p*-nitrophenyl maltoheptaoside (BPNPG7) containing a *p*-nitrophenyl group at the reducing end of maltoheptaoside, with a 4,6-linked-*O*-benzylidine group at the non-reducing end [51]. Hydrolysis of this produces an easily measured yellow colour.

In addition to the in vitro enzymic assays, the Caco-2 cell line, originating from a human colon adenocarcinoma, is often used as a model for the small intestine since it expresses sucrase, maltase and lactase on its brush border, albeit at lower levels than the small intestine in vivo. At conditions of confluence, the cells differentiate into small intestine-like cells expressing these enzymes and their activities plateau about 10–20 days after confluence [52]. Expression of GLUT1, GLUT2, GLUT3, GLUT5 and SGLT1 mRNAs in Caco-2 cells

 

varies between clones and depends on the cell growth phase and glucose consumption rates [53, 54]. The transfer of glucose from the apical (gut lumen) side into the cells indicates the amount of glucose that passes through the apical membrane, and how this process might be inhibited. The measurement of glucose transfer from the apical to the basolateral side is an indication of how much glucose might be absorbed, and how polyphenols might inhibit this process. For ease of measurement and accuracy, radiolabelled glucose is the most robust method since it is not influenced by endogenous glucose [55].

## 8 Influence of polyphenols on starch digestion

Extracts from tea inhibited salivary α-amylase both in vitro and in humans in vivo, proposed to lower the cariogenicity of starch-containing foods [56, 57]. Black tea, especially theaflavins and gallate esters, were most effective, but not (–)-epicatechin or (–)-epigallocatechin, and inhibited human salivary α-amylase with micromolar inhibition constants by a non-competitive mechanism [58]. Strawberries showed no inhibitory activity against porcine pancreatic α-amylase with detection of starch hydrolysis by dinitrosalicylic acid [59]. Quercetagetin, scutellarein and fisetin inhibited human salivary α-amylase acting on potato starch with detection by the Nelson-Somogyi reagent, with $IC_{50} < 0.02$ mM, compared to acarbose at 0.001 mM. These inhibition constants correlated with predictions derived from in silico docking into the enzyme active site where the important interactions were due to hydrogen bonds between the hydroxyl groups of the polyphenol ligands and the catalytic residues of the binding site, and formation of a conjugated π system [60]. The chlorogenic acid, 5-caffeoylquinic acid, inhibited purified pig pancreatic α-amylase with $IC_{50} < 0.1$ mM, with *p*-nitrophenyl-α-D-maltoside as substrate. 5-caffeoylquinic acid was ∼4–5 times more potent than caffeic acid alone (quinic acid was not relevant at dietary levels), with the mechanism as mixed type [61]. Berry polyphenols inhibit pig pancreatic α-amylase, especially extracts from raspberry and rowanberry, with one of the active components proposed to be proanthocyanidins. Strawberry and lingonberry extracts were also active, but with much weaker activities to those of pomegranate, blueberry and red wine, assayed using gelatinised potato starch with detection of reducing groups using hydroxybenzoic acid hydrazide. The inhibition was synergistic with acarbose [62, 63].

Proline-rich proteins are present at high concentrations in saliva and are able to bind to many polyphenols, especially galloylated and polymeric ones [64, 65] and, in the Caco-2 model, may influence the absorption of polyphenols by a small amount [66]. Proline-rich proteins may also decrease the extent of inhibition of digestive enzymes by polyphenols [67] although this potentially important interaction has not been widely studied. Salivary proteins may also act to solubilise polyphenols and increase their accessible concentration [68].

## 9 Influence of polyphenols on disaccharidases

Inhibition of sucrase in situ is a difficult assay to conduct appropriately since the enzyme is membrane-bound in the intestine and is only expressed at low levels in Caco-2 cells. Intestinal preparations such as acetone extracted proteins from rat intestine can be used as a source of enzyme as this is commercially available. The hydrolysis of the substrate, sucrose, is most commonly measured by quantification of the product, glucose. Some assays have employed *p*-nitrophenyl-glucoside as a substrate together with the intestinal extract, but this is not specific for sucrase, and only indicates a general α-glucosidase activity. The *p*-nitrophenol release from such substrates is easy to measure, and has been performed by several authors. However, here I will only consider data from experiments using the real substrate, sucrose, to indicate sucrase activity, or maltose to measure maltase activity.

Baicalein derivatives inhibited sucrase as measured using a rat intestinal extract, sucrose as substrate and detection of glucose using glucose oxidase [69, 70]. Using similar assays, cyanidin-3-*O*-rutinoside inhibited sucrase with $IC_{50}$ 0.25 mM [71] and maltase with $IC_{50}$ of 2.3 mM [71], cyanidin-3-*O*-galactoside and cyanidin-3-*O*-glucoside inhibited with $IC_{50}$ values of 0.5 and 0.3 mM respectively [72], chebulinic acid and chebulagic acid, low molecular weight tannins, inhibited maltase with $IC_{50}$ of 0.036 and 0.007 mM respectively, but neither inhibited sucrase nor isomaltase activities [73, 74]. Cyanidin-3-*O*-rhamnoside and pelargonidin-3-*O*-rhamnoside, from Acerola fruit, weakly inhibited rat intestinal sucrase and maltase activities with $IC_{50}$ values $> 4$ mM as measured using intestinal extracts with detection of hydrolysis using HPLC with refractive index detection [75]. Theasinensin A and B, strictinin, catechin, theaflavin and 1,6-digalloyl glucose inhibited maltase activity quite effectively, but were ineffective against sucrase [76].

## 10 Influence of polyphenols on glucose absorption

Several reports have indicated that polyphenols interact with sugar transporters in various ways. Using GLUT2 expressed in Xenopus Oocytes, myricetin, fisetin and quercetin were shown to inhibit transport of glucose and fructose in a non-competitive manner with $IC_{50}$ values of 0.017, 0.047 and 0.013 mM, respectively. Quercetin-3-*O*-glucoside was also an inhibitor (0.064 mM) but no other glycosides were tested in this system. Under the same conditions, GLUT5 and SGLT1 were not affected [77, 78]. Quercetin glucosides inhibited glucose transport into brush border membrane vesicles of pig jejunum [79]. Fisetin, myricetin and quercetin were

 

also the most potent of those tested for inhibition of glucose transport into myelocytic U937 and lymphocytic Jurkat cells [80]. Naringenin inhibits renal transport of glucose [45] and several phenolics inhibited glucose uptake in rat intestinal brush border membrane vesicles [81]. Most of these studies have examined aglycone forms. These are not present in food, but would be present after action of LPH in the gut, which hydrolyses glucosides of many flavonoids [38]. However, given the typical $IC_{50}$ values or inhibition constants, flavonoids are potent enough to act in the gut where concentrations can reach millimolar levels (Table 1), but not in the blood and tissues where concentrations are generally less than 0.005 mM.

Several studies have also examined the effects of polyphenols on glucose transport across the intestine using intact cellular models, especially Caco-2 cells. Here, two parameters can be measured, the amount of glucose that appears inside the cells, as a result of apical uptake, and the amount that appears in the basolateral side, indicating the amount that passes through the apical and basolateral sides. Uptake of radiolabelled glucose into Caco-2 cells was inhibited by green tea polyphenols with inhibition of both SGLT1 and GLUT2. At 0.1 mM, (–)-epigallocatechin gallate gave ~50% inhibition, (–)-epigallocatechin and (–)-epicatechin gallate about 80% inhibition. As expected, phlorizin inhibited SGLT1-dependent uptake, whereas the aglycones quercetin and myricetin inhibited GLUT2-dependent uptake [82]. Although the green tea polyphenol (–)-epicatechin gallate inhibited SGLT, it was not transported by it [83]. In the intestine, glucose is transported from the apical to the basolateral side, so crossing two biological membranes (Fig. 1). Quercetin-3-*O*-rhamnoside, phlorizin, pelargonidin-3-*O*-glucoside and 5-caffeoylqunic acid all inhibited this transfer from the apical to the basolateral side, primarily by inhibition of GLUT2 with less inhibition of SGLT1 [55]. Strawberry and apple extracts also inhibited this apical to basolateral transfer [55]. Phlorizin can not only inhibit SGLT1 but the aglycone phloretin after hydrolysis can blockade GLUT2, which is likely to assume greater importance even at low luminal glucose concentrations following SGLT1 inhibition. Phlorizin in commercial apple juice when consumed by volunteers modified glucose tolerance and gastrointestinal hormone secretion [84].

## 11 Estimation of importance of polyphenols and example of acarbose

Since polyphenols are multifunctional dietary components, the effect of their action on carbohydrate digestion and absorption is only one of their proposed activities. To estimate the importance of this aspect of polyphenols, it can be useful to examine the magnitude of the effect of a drug, which is not absorbed and has a comparable action on carbohydrate digestion and absorption. Acarbose is an inhibitor of α-glucosidases and is not absorbed, so is an excellent example of how efficient the action of compounds, which work only in the gut post-prandially, might be. In a test with 118 participants, who took acarbose for 3 years, the absolute risk reduction for diabetes was 6% (95% CI: –9; 2). The mean difference of the post-load plasma glucose after 3 years was –1.16 mmol/L (95% CI: –2.03; –0.17) with no effect on insulin secretion and insulin sensitivity [85]. Acarbose reduced post-prandial hyperglycemia with an 0.8% decrease in HbA1c according to Cochrane meta-analysis. Acarbose decreased the incidence of diabetes by 36%, improved flow mediated vasodilation and reduced progression of intima media thickness. In a meta-analysis on type II diabetic patients, acarbose treatment was associated with a 64% lower rate of myocardial infarction and 35% less cardiovascular events [86]. Acarbose therapy reduced the risk of a cardiovascular event in 1429 individuals with IGT by 49% ($p = 0.03$), reduced the risk of an acute myocardial infarction by 91% ($p = 0.02$) and of developing hypertension by 34% ($p = 0.006$) [87].

## 12 Conclusions

The presence of polyphenols in the diet will undoubtedly influence the apparent glycemic index of foods and consequently the extent of post-prandial blood glucose excursions, and this effect occurs almost throughout the entire lifetime. This effect is through inhibition of sugar metabolising enzymes and transporters. What is not certain at the moment is how much difference this makes to diabetes risk, although epidemiological studies tend to support the protective effect of polyphenol-rich foods and beverages against development of type II diabetes. The potential of this aspect of polyphenol action is apparent from the biological effects of acarbose, which acts by the same mechanism as proposed here for polyphenols, and significantly reduces diabetes risk in chronic intervention studies. The most promising effects will probably be derived from foods, which contain compounds able to modulate more than one of the described pathways, leading to possible synergies.

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