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Dietary (poly)phenols mitigate the risk of metabolic disease via gut mechanisms

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Delaying carbohydrate digestion and glucose absorption, via inhibition of gastrointestinal α-amylase, α-glucosidase and glucose transporter activities, is an effective strategy to alleviate postprandial hyperglycaemia, which is a major risk factor for the development of insulin resistance and metabolic diseases such as type 2 diabetes. Oral antihyperglycaemic agents (OHAs) can be used alone or in combination with other medications or insulin to manage diabetes. However, OHAs are associated with a risk of hypoglycaemic events and numerous side effects, especially gastrointestinal symptoms, and are contraindicated in patients with irritable bowel syndrome and/or kidney, liver or cardiac dysfunction[(1)]. Hence, there is interest in food-based compounds, such as (poly)phenols, with similar but milder effects to reduce hyperglycaemia and risk of metabolic disease, and to manage diabetes. Our complete and highly sensitive *in vitro* protocol can measure human carbohydrate digestive enzyme activities[(2)] and glucose transport[(3)]accurately. The sugars in enzyme assays (both substrates and products) and transcellular glucose transport assays (including lactulose, which is added as a control for cell monolayer integrity) are quantified directly by specialised ion chromatography. We use commercially-available human α-amylases to assess starch hydrolysis and brush border α-glucosidases derived from differentiated human intestinal Caco-2/TC7 cells to assess disaccharide hydrolysis, while 2-deoxy-D-glucose transport is measured across Caco-2/TC7 cell monolayers cultured on transmembrane supports. Enzyme and glucose transporter activities are measured in the presence of various concentrations of phenolic compounds or phenol-rich extracts and compared to the controls using one-way ANOVA. The potency of potential inhibitors is evaluated by calculating the half-maximal inhibitory concentration (IC_{50}). We have successfully used this protocol to screen for potential inhibition by dietary (poly)phenols and uncover specific mechanisms of action and structure-function relationships. For example, we confirmed that quercetagetin, a polyphenol in spinach, inhibits human salivary α-amylase by binding to both starch and the enzyme ($p < 0.05$ vs quercetagetin-free control; $IC_{50} = 30.1 \pm 2.1$ μM), while also inhibiting human α-glucosidase activities. Anthocyanidins found in berries directly inhibit pancreatic α-amylase ($p < 0.05$ vs anthocyanidin-free control), especially peonidin ($IC_{50} = 25.8 \pm 1.9$ μM) and petunidin ($IC_{50} = 28.5 \pm 0.8$ μM), while polyphenols found in walnut inhibit both salivary and pancreatic α-amylases and intestinal glucose transport. Notably, we have identified several plant-derived inhibitors that may be useful in regulating postprandial glycaemia *in vivo*. Such mechanisms may partially explain why a diet that is high in fruits and vegetables results in lower metabolic disease risk. Dietary (poly)phenols offer the potential to manage insulin resistance by diet and adjunct therapies with lesser side effects than OHAs. Further, our accurate and reliable method will benefit researchers involved in the discovery and development of novel agents for the prevention and management of diabetes.

References

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