In silico docking and ADMET studies on clinical targets for type 2 diabetes correlated to *in vitro* inhibition of pancreaticalpha-amylase and alpha-glucosidase by rutin, caffeic acid, p-coumaric acid, and vanillin

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Background: *Diabetes mellitus* affects millions of people worldwide and if left untreated leads to many serious complications such as hypertension, stroke, coma, or even death, (Sharma, 2018). Although drugs are commercially available, often these are unaffordable and have undesirable side effects. Therefore, to discover new and more effective treatments is of importance. Several edible plants have been found to have antidiabetic properties and the molecules contributing to activity may be an alternative source of molecules for the treatment of type 2 diabetes (T2D), (Pereira *et al.*, 2019). The aim of this study was to analyse the *in silico* properties and the digestive enzyme inhibition ability of selected compounds present in herbs, spices, and medicinal plants.

Methods: The inhibition of pancreatic alpha-amylase and alpha-glucosidase would decrease hyperglycemia for the management of type 2 diabetes. This study focuses on the compounds in commercially available herbs and spices and their ability to inhibit pancreatic alpha-amylase and alpha-glucosidase. These compounds were rutin, caffeic acid, p-coumaric acid, vanillin, ethyl gallate, and oxalic acid. The binding affinity of the compounds in herbs and spices was evaluated using a virtual docking simulation known as Glide and the ADMET properties were predicted using pKCSM. Six compounds with a range of docking scores were subjected to enzyme kinetic studies using *in vitro* pancreatic alpha-amylase and alpha-glucosidase biochemical assays. Acarbose, a prescribed alpha-amylase and alpha-glucosidase inhibitor, was used as a positive control.

Results: There was a strong correlation between the *in silico* and *in vitro* results where a more negative docking score was associated with a smaller inhibition constant (Ki). Caffeic acid, vanillin, ethyl gallate, and p-coumaric acid had Ki values that were similar to ($p > 0.05$) to the Ki of acarbose (Ki = 14±1 µM) for pancreatic alpha-amylase. Rutin, caffeic acid, vanillin, and p-coumaric acid had Ki values that were similar to ($p > 0.05$) the Ki of acarbose (Ki = 481±43 µM) for alpha-glucosidase. The cell viability of these compounds was assessed with the sulforhodamine B (SRB) assay in Caco2 cells. Caffeic acid, p-coumaric acid, rutin, and vanillin in the Caco2 cell line (intestinal epithelial cell model) had IC_{50} values that were similar ($p > 0.05$) to acarbose (IC_{50} = 715±89.1 µM); whereas ethyl gallate and oxalic acid, the IC_{50} values were significantly ($p < 0.05$) greater than acarbose. Rutin, caffeic acid, p-coumaric acid, and vanillin had similar inhibitory activity as acarbose for pancreatic alpha-amylase and/or alpha-glucosidase. Ethyl gallate and oxalic acid were more cytotoxic to Caco2 cells.

Conclusions: Rutin, caffeic acid, p-coumaric acid, and vanillin could regulate hyperglycemia for management of type 2 diabetes. Herbs and spices have several benefits over prescription drugs such as acarbose. The benefits include being less expensive, easier to obtain, and having fewer side effects. The amount of herb or spice that contains the amountof rutin, caffeic acid, or vanillin equivalent to the 150 mg daily dose of acarbose is 5 g parsley, 4 g common verbena,and 2 g vanilla. The presence of several inhibitory compounds in a single herb or spice is most advantageous when it comes to complementary and alternative medicines because each compound could have different modes of action and can act synergistically. In addition, when used in combination with antidiabetic drugs may have a beneficial effect.

References:

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