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Dietary phytochemicals as regulators of gut inflammation in the context of type 2 diabetes

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Numerous disorders, including type 2 diabetes and even COVID-19, are linked to poor gut health and inflammation[1,2]. In addition to impacting food digestion and absorption, gut inflammation worsens diabetes outcomes by causing gut microbial dysbiosis, disrupting tight junctions (allowing microbial metabolites to freely enter into circulation), and altering glucose absorption[3]. ACE2 is a crucial regulator of gut health and has received much attention during the COVID-19 pandemic due to its role as a major viral entry protease. Studies have shown that the ACE2/Ang-(1-7)/Mas axis is important in managing inflammation and maintaining normal glucose metabolism[3]. Dietary phytochemicals are plant bioactive compounds, with promising anti-inflammatory and anti-diabetic properties, and may affect these processes. In this work, we aimed to look at the link between inflammation, ACE2 and the glucose transporters, SGLT1 and GLUT2, and how phytochemicals could be used to normalise the changes brought about by inflammation in Caco-2/TC7 human intestinal epithelium cells. We first examined how gut inflammation, ACE2 and glucose transporters are related and proceeded to look at the effect of some chosen phytochemicals on regulating glucose transport via modulation of the ACE2/Ang(1-7)/Mas axis. This included genistein (an isoflavone from soyabeans), sulforaphane (an isothiocyanate found in Brassica, especially broccoli), apigenin (a flavone found in vegetables and herbs), and artemisinin (a sesquiterpene lactone used as a drug). The impact of phytochemicals on the SARS-CoV-2 viral entry receptors, ACE2 and TMPRSS2, was also examined as a secondary outcome. To induce inflammation, the Caco2/TC7 cells were co-stimulated with IL-1β (25 ng/mL) and TNF-α (50 ng/mL) for varying durations (24 h, 48 h, 72 h, 168 h) and changes in target gene expression (ACE2, SGLT1, GLUT2, TMPRSS2) were assessed by droplet digital PCR. IL-6 and IL-8 were assessed as markers of inflammation in the cell culture media by multiplex ELISA. Inflammation increased ACE2, TMPRSS2 and SGLT1 mRNA. ACE2 increased with cytokine exposure duration, coupled with an obvious decrease in IL-8, SGLT1 and TMPRSS2. Pearson correlation analysis revealed that the increase in ACE2 was strongly associated with decreases in SGLT1 ($r = -0.99$, $p<0.01$) and IL-8 ($r = -0.959$, $p<0.05$), implying ACE2 to play a crucial role in gut inflammation and postprandial glycaemia. After establishing the gut cell inflammation model, we compared the effect of the phytochemicals on our target genes in cells cultured in normal and pro-inflammatory environments. None of the tested phytochemicals were effective in reducing IL-8 secretion, while phytochemicals showed varying effects on the target genes. Genistein normalised the effects of inflammation on the target genes with less effect from the other tested phytochemicals. However, further research is required to assess the importance of genistein *in vivo* in the context of gut inflammation and type 2 diabetes.

Keywords: ACE2; glucose transporters; COVID-19; Genistein.

Ethics Declaration

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