In vitro and *in silico* Antidiabetic Effects of Selected Flavonoids: Molecular and Structure-Activity Relationships

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Abstract: Numerous *in vitro*, *in silico* and *in vivo* studies have revealed antidiabetic potential of flavonoids. The biological properties of these polyphenolic flavonoids are in fact structure dependent, though not thoroughly understood yet. Therefore, the aim of this work was to evaluate the in vitro antidiabetic properties of 14 structurally related polyphenolic compounds to verify the critical positions responsible, their correlation, as well as the effect of derivatization on the same properties. Initially, 14 selected flavonoids were subjected to cytotoxicity tests on RIN-5F pancreatic and 3T3-L1 preadipocytes cell lines. Then, all flavonoids were subjected to *in vitro* antidiabetic investigation at the lowest dose (0.39 ug/ml) using RIN-5F to evaluate the insulin secretagogue property via ELISA as well as on 3T3-L1 adipocytes to evaluate the insulin sensitizing property through adipogenesis and fluorescence glucose uptake assays. Subsequently, adipokines such as leptin, tumor necrosis factor-α (TNF-α), adiponectin, and retinol binding protein-4 (RBP-4) were measured to evaluate the biochemical reactions. Western blotting was then performed to determine GLUT4, PPARγ and PPARα protein expressions. To further understand the mechanism, a molecular docking study was performed against the a-glucosidase and GLUT 1 proteins. The results revealed that the total number and the configuration of hydroxyl groups, the presence of C2-C3 double bond as well as C4 ketonic group play chief roles in regulating antidiabetic activity which helps to enhance the glucose uptake via PPAR and GLUT4 protein receptors. The results obtained may help for the development of synthetic analogs retaining substantial antidiabetic effect.

Keywords: Antidiabetic; Flavonoids; Structure Activity Relationship