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Flavonoid c-glycosides as leads against PTP1B in type 2 diabetes therapy

Protein tyrosine phosphatase 1B (PTP1B), a negative regulator of the insulin signaling pathway has gained attention as a validated druggable target in the management of type 2 diabetes mellitus (T2DM), a global epidemic threatening human health. The lack of a clinically approved PTP1B inhibitors has continued to prompt research in plant-derived therapeutics possibly due to their relatively lesser toxicity profiles and ease of accessibility. Flavonoid-c glycosides are one of the plant-derived metabolites gaining increased relevance as anti-diabetic agents, albeit the possible mechanism of action remains largely unknown. This study investigates the anti-diabetic potential of the flavonoid c-glycosides against PTP1B in silico and in vitro. Of the seven flavonoid c-glycosides docked at the active site of the enzyme, three compounds (apigenin, vitexin and orientin) had the best affinity for the enzyme with a binding score of − 7.3 kcal/mol each, relative to − 7.4 kcal/mol for the standard, ursolic acid. A further probe into the degree of structural flexibility, stability, and compactness of the resulting complexes for the three compounds over a 26 ns dynamics simulation period suggested orientin as the most prominent PTP1B inhibitor with an overall binding energy of − 27.91 kcal/mol compared to − 37.55 kcal/mol for the standard. This observation was consistent with the results of the in vitro evaluation, where orientin had a half maximal inhibitory concentration (IC50) of 0.18 mg/ml relative to 0.13 mg/ml for the standard. Put together, while the results suggest that orientin a potential PTP1B inhibitor could be further explored as a promising therapeutic agent in the management of T2DM, it has also lent scientific credence to its possible mechanism of antidiabetic action through establishment and modulation of molecular interactions towards the catalytic amino acid residues at the active site of PTP1B.

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