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Dual incretin-modulating effects of Roselle (*Hibiscus sabdariffa*) extract and its flavonoids in experimental type 2 diabetes

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Abstract

Background: Altered incretin signaling, characterized by reduced GLP-1 secretion and enhanced DPP-4 activity, drives the pathogenesis of T2DM. Roselle (*Hibiscus sabdariffa*) is rich in bioactive flavonoids, which may potentially modulate the incretin pathway.

Methods: The crude extracts and ethyl acetate subfractions of Roselle were assessed for DPP-4 inhibitory activity and GLP-1 secretion by using enzyme-based assays and STC-1 cell-based HTRF assays. Bioactivity-guided fractionation and HPLC profiling identified quercetin and myricetin as major active constituents. Molecular docking analysis was conducted to examine the interaction of flavonoids with the DPP-4 catalytic site. Mechanistic studies employed pharmacological inhibitors targeting bitter taste receptor associated signaling pathways including PLC, ROCK, and intracellular Ca^{2+} mobilization. The in vivo efficacy of Roselle extracts was examined in a high-fat diet/low-dose streptozotocin-induced C57BL/6 mouse model of T2DM.

Results: Roselle extract showed potent DPP-4 inhibition and stimulated glucose-dependent GLP-1 secretion, which was more effective in the quercetin-rich fractions. Docking analysis supported stable binding of flavonoids within the DPP-4 active pocket. GLP-1 secretion significantly reduced by inhibitors of the pathway, suggesting the involvement of bitter taste receptor–mediated PLC–IP_3–ROCK–Ca^{2+} signaling. In diabetic mice, Roselle treatment improved fasting glycemia, decreased triglyceride levels, increased oral glucose tolerance, increased circulating GLP-1 levels, and decreased plasma DPP-4 activity.

Conclusion: Roselle exhibits dual incretin-modulating actions through the inhibition of DPP-4 directly and stimulation of GLP-1 secretion mediated by the bitter taste receptor, which was indicative of its potentiality to function as a plant origin therapeutic approach in T2DM management.

Keywords: Roselle, GLP-1, DPP-4 inhibition, Polyphenolic flavonoids, Type 2 diabetes mellitus, Incretin signaling

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