Abstract:

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, impaired insulin secretion, and elevated blood glucose levels. While conventional antidiabetic therapies primarily offer symptomatic relief, they often fail to address the underlying oxidative and inflammatory processes contributing to disease progression. Polyphenolic compounds, a class of bioactive molecules abundantly present in plant-based foods, have emerged as promising multitarget agents for diabetes management due to their potent antioxidant, anti-inflammatory, and insulin-sensitizing properties.

This study investigates the therapeutic potential of polyphenolic compounds in T2DM by focusing on their interactions with three critical molecular targets—AMP-activated protein kinase (AMPK), glucose transporter type 4 (GLUT4), and peroxisome proliferator-activated receptor gamma (PPAR-γ). These targets play vital roles in regulating glucose uptake, lipid metabolism, and insulin sensitivity. A comprehensive literature review was followed by the selection and screening of 100 polyphenolic compounds based on pharmacokinetic criteria, from which 30 were shortlisted for molecular docking studies.

Molecular docking was performed using AutoDock Vina integrated in PyRx, with structural visualization in BIOVIA Discovery Studio. Target protein structures were retrieved from the Protein Data Bank (PDB), and docking simulations were conducted to assess binding affinities and interaction profiles. The results demonstrated strong binding affinities of selected polyphenols—such as resveratrol, quercetin, naringenin, hesperetin, catechin, genistein, and formononetin—with AMPK, GLUT4, and PPAR-γ, indicating their capacity to activate or modulate these receptors effectively.

Further validation was conducted through analysis of existing in vitro, in vivo, and clinical trial data. Compounds like resveratrol and naringenin were shown to significantly improve glycemic control, reduce oxidative stress, and enhance insulin sensitivity in both preclinical models and human studies. The docking scores correlated well with reported biological activity, strengthening the case for their therapeutic potential. Notably, the binding energies for some polyphenols were comparable to or even surpassed those of standard antidiabetic drugs, underscoring their relevance as adjunct or alternative therapies.

This integrated computational and experimental review highlights the potential of select polyphenolic compounds as multifaceted agents for T2DM management. By targeting AMPK, GLUT4, and PPAR-γ simultaneously, and offering antioxidant protection, these compounds provide a holistic approach to glycemic control and metabolic regulation. However, limitations such as poor bioavailability, limited clinical translation, and lack of formulation strategies remain. Future research should focus on optimizing delivery systems, improving pharmacokinetics, and conducting large-scale clinical trials to establish their efficacy and safety. Ultimately, the incorporation of polyphenolic compounds into clinical practice could pave the way for safer, natural, and more effective diabetes therapies.