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Insights from *in silico* exploration of major curcumin analogs targeting human dipeptidyl peptidase IV

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ABSTRACT

The goal of this work is to use a variety of in-silico techniques to identify anti-diabetic agents against DPP-IV enzyme from five main curcumin analogues. To produce the successful molecules, five main curcumin analogues were docked into the active site of DPP-IV enzyme. In comparison to the control molecule (Saxagliptin, −6.9 kcal/mol), all the compounds have the highest binding affinity (-7.6 to −7.7 kcal/mol) for the DPP-IV enzyme. These compounds underwent further testing for studies on drug-likeness, pharmacokinetics, and acute toxicity to see the efficacy and safety of compounds. To assess the stability of the docking complex and the binding posture identified during the docking experiment, our study got THC as the lead compound, which was then exposed to 200 ns of molecular dynamic simulation and PCA analysis. Additionally, DFT calculations were conducted to determine the thermodynamic, molecular orbital, and electrostatic potential characteristics of lead compound. Overall, the lead chemical has shown strong drug-like properties, is non-toxic, and has a sizable affinity for the DPP-IV enzyme.

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KEYWORDS
Anti-diabetic; curcumin; in-silico; docking; MD simulation; DFT

1. Introduction

The most prevalent endocrine and chronic illness in people is thought to be diabetes mellitus (DM) which is linked to the abnormal blood glucose levels of body (Oyebode et al., 2018). According to Keska et al, it is a member of the class of non-communicable diseases (NCDs) brought on by metabolic abnormalities (Kęska et al., 2019). Globally, diabetes was directly responsible for at least 1.5 million fatalities in 2015 alone, according to the World Health Organization (WHO, 2016). One of the most prevalent health issues affecting individuals worldwide roughly 422 million individuals with DM in 2014 (Kęska et al., 2019) nearly a fourfold rise in patients over the previous thirty years.

The two main kinds of diabetes are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with T2DM being far more prevalent and accounting for 90%–95% of all occurrences. The very intricate interactions between genetic systems and environmental variables are at the root of the T2DM pandemic. Some of them are amenable to behavioral modification, such as by adopting an adequate diet and leading a healthy lifestyle, making DM prevention and treatment successful. Inhibiting metabolic enzymes such alpha-amylase, alpha-glucosidase, or dipeptidyl peptidase IV (DPP-IV) that are involved in controlling blood sugar levels is another therapeutic approach (Kęska et al., 2019). One of the major health issues in the current world is the rising prevalence of T2DM. As a result, new approaches to problem resolution are urgently needed to evaluate early metabolic problems, including insulin resistance (Ponnulakshmi et al., 2019).

PTP-1B, glucokinase, DPP-IV, peroxisome proliferator-activated receptor, aldose reductase, insulin receptor, etc. are some of the enzymes that are crucial in T2DM (Saeed et al., 2021). Among them, DPP-IV is a serine protease enzyme that is in charge of the quick breakdown of the incretin's glucagon-like peptide 1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP). The intestinal mucosa produces incretins, namely GIP and GLP-1, which promote glucose-induced insulin release and reduce blood glucose concentrations. The incretin pathway, which is activated by GLP-1 and GIP, is responsible for around 60% of the body's insulin secretion. As a result, there are basically two ways that GLP-1 treatments have been utilised to treat diabetes. According to Okechukwu et al, both therapies work to prolong the duration that GLP-1 circulates in the liver (Okechukwu et al., 2020).

Due to their numerous pharmacological and biological uses, natural products have evolved into an alternative and supplemental therapeutic method. A vast spectrum of phytoconstituents and pharmacological properties are present in medicinal

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