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ORIGINAL PAPER

In Silico Exploration of Isoxazole Derivatives of Usnic Acid: Novel Therapeutic Prospects Against α-Amylase for Diabetes Treatment

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Abstract

Diabetes mellitus (DM) a metabolic disorder characterized by high blood sugar levels causing damage to various organs over time. Current anti-diabetic drugs have limitations and side effects, prompting a search for new inhibitors targeting the α-amylase enzyme. This study aims to discover such inhibitors from thirty isoxazole derivatives of usnic acid using in silico approaches. The potential inhibitory effects of compounds were investigated using ADMET, molecular docking, molecular dynamic simulation, principal component analysis and density functional theory studies. ADMET analysis exhibited a wide range of physicochemical, pharmacokinetic, and drug-like qualities with no significant side effects which were then investigated using molecular docking experiment to determine the lead compound with the best binding affinity for the α-amylase enzyme. All compounds showed good binding affinity against α-amylase enzyme (−7.9 to −9.2 kcal/mol) where compound-13 showed the best binding affinity of −9.2 kcal/mol forming hydrogen bonds with Leu162, Tyr62, Glu233 and Asp300 amino acids. Furthermore, the binding posture and the stability of the compound-13-α-amylase enzyme complex was confirmed by molecular dynamic simulation experiment. Moreover, compound-13 showed binding energy value of −27.92 ± 5.61 kcal/mol, which indicated it could be an α-amylase inhibitor. Additionally, the reactivity of compound-13 was further confirmed by density functional theory analysis. The above findings suggest compound-13 to be a potential α-amylase inhibitor in DM. And setting the stage for further in vitro and in vivo experimental validation.

Keywords Anti-diabetic · α-amylase · docking · MD Simulation · DFT

Introduction

Diabetes mellitus (DM) is a collective term for a series of chronic metabolic illnesses characterised by hyperglycemia brought on by abnormalities in insulin action, production, or both [1]. Common types of DM can result in macrovascular endpoints including ischemic heart disease, stroke, and peripheral vascular disease, as well as microvascular endpoints like retinopathy, nephropathy, and neuropathy, which can cause multisystem consequences [2]. The global count of diabetic patient was 462 million during 2022 [3] and is predicted to be 578 million by 2030 [4, 5]. The World Health Organization (WHO) estimatesd a rise to 642 million cases of DM by 2040, worldwide [6]. Antidiuretic interventions provide patients varying degrees of effectiveness. These include: (1) insulin secretagogues; (2) substances that can lower insulin resistance; and (3) inhibitors of the digestive enzymes that process carbohydrates [7]. On the other hand, concomitant adverse effects include

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