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ORIGINAL RESEARCH

Virtual screening of pyrazole derivatives of usnic acid as new class of anti-hyperglycemic agents against PPARγ agonists

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Abstract

The finest sources of therapeutic agents are natural products, and usnic acid is a secondary metabolite derived from lichen that has a wide range of biological actions, including anti-viral, anti-cancer, anti-bacterial, and anti-diabetic (hyperglycemia). Based on the hyperglycemia activity of UA, this work seeks to identify new anti-hyperglycemia medicines by virtual screening of pyrazole derivatives of UA. Seven hit compounds (Compounds 1, 5, 6, 7, 17, 18 and 33), which finally go through docking-based screening to produce the lead molecule, were identified by the physicochemical attributes, drug-likeliness, and ADMET prediction. The docking score for the chosen compounds containing PPARγ agonists ranged from -7.6 to -9.2 kcal/mol, whereas the docking goal for compounds 5, 6, and 7 was -9.2 kcal/mol. Based on the binding energy and bound amino acid residues as well as compared to the reference compound, compound-6 considered as lead compound. Furthermore, the MD simulation of 3CS8-Compound-6 and 3CS8-Rosiglitazone complexes were performed to verify the stability of these complexes and the binding posture acquired in docking experiments. The compound-6 had strong pharmacological characteristics, bound to the PPARγ agonist active site, and was expected to reduce the activity of the receptor, according to the virtual screening results. It must be justified to conduct both *in-vitro* and *in-vivo* experiments to examine the efficacy of this compound.

Keywords Virtual screening · Usnic acid · Anti-hyperglycemic · PPARγ agonists · Docking · MD Simulation

Introduction

Diabetes-related hyperglycemia and associated cardiovascular and renal consequences are major causes of death and high healthcare costs. It has been demonstrated that hyperglycemia encourages glomerular hyperfiltration, a condition associated with diabetes and obesity and a precursor to chronic kidney disorders (Amin et al. 2018). It might exacerbate renal problems over time by causing uremic toxicity, oxidative stress, inflammation, and hypertension. It has been demonstrated that controlling hyperglycemia greatly reduces the prevalence of renal disorders. Therefore, any strategy to reduce hyperfiltration or hyperglycemia will be helpful. According to Ibrahim et al. 2017, PPARs are nuclear hormone receptor superfamily ligand activated transcription factors. The control of lipid and glucose homeostasis is regulated by three PPAR isotypes, known as PPAR α, δ and γ (Janani and Kumari 2015). The development of insulin-sensitizing anti-hyperglycemic drugs must consider the vital roles that PPARγ plays in the metabolism of glucose and the storage of fatty acids (Ibrahim et al. 2017).

Natural products (NPs) have played a significant role in medication development throughout human history as a means of treating a variety of illnesses. Natural products made up 67% of the 1562 small molecules on the market that the US Food and Drug Administration (FDA) had authorized between 1981 and 2014 (Newman and Cragg 2016). There may be interest in using natural goods and the components in them as a form of alternative therapy.

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