VIRTUAL SCREENING VIETNAMESE NATURAL PRODUCTS FOR TREATMENT OF DIABETES MELLITUS

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GENERAL INFORMATION

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ABSTRACT

Medicinal plants have been known and used as a rich source of therapeutic agents all over the world. It has been known that several natural products are important treatments against diabetes mellitus. Human islet amyloid peptide (hIAPP1–37) aggregation is an early step in diabetes mellitus because hIAPP aggregates in type II diabetics to form oligomers that interfere with beta-cell function, eventually leading to the loss of insulin production. In this study, we have collected 342 compounds derived from Vietnamese natural products and investigated their binding affinity to hIAPP1–37 peptide using molecular docking technique. The results show that five drug candidates with the strongest binding affinity are Solasodine (-9.4 kcal/mol), Diosgenin (-9.2 kcal/mol), Sarsasapogenin (-9.1 kcal/mol), Peiminine (-8.9 kcal/mol) and Hecogenin (-8.7 kcal/mol). Among them, Solasodine forms the hydrogen bond with the amino acids Arg11, Hecogenin also creates the hydrogen bond with Asn31, meanwhile Peiminine had two hydrogen bonds with Asn22 and Asn31. Hydrophobic interactions formed by these compounds with residues Arg11, Phe15, Asn21, Ala25 were found to be essential for the stability of the ligand–protein complex.

TÓM TẮT

Cây thuốc đã được biết đến và sử dụng như một nguồn dữ liệu phong phú các tác nhân trị liệu trên toàn thế giới. Người ta đã biết đến một số hợp chất tự nhiên được dùng như phương pháp điều trị quan trọng chống lại bệnh đái

tháo đường. Sự tổng hợp peptide amyloid đảo nhỏ ở người (hIAPP1–37) là một bước đầu tiên trong bệnh đái tháo đường vì hIAPP tập hợp ở bệnh nhân tiểu đường loại II để tạo thành oligomer can thiệp vào chức năng tế bào beta, cuối cùng dẫn đến mất sản xuất insulin. Trong nghiên cứu này, chúng tôi đã thu thập được 342 hợp chất có nguồn gốc từ các sản phẩm tự nhiên của Việt Nam và khảo sát ái lực liên kết của chúng với hIAPP1–37 peptide bằng kỹ thuật ghép nối phân tử. Kết quả cho thấy 5 ứng cử viên thuốc có ái lực liên kết mạnh nhất là Solasodine (-9,4 kcal/mol), Diosgenin (-9,2 kcal/mol), Sarsasapogenin (-9,1 kcal/mol), Peiminine (-8,9 kcal/mol) và Hecogenin (-8,7 kcal/mol). Trong đó, Solasodine tạo liên kết hydro với axit amin Arg11, Hecogenin cũng tạo liên kết hydro với Asn31, trong khi Peiminine có 2 liên kết hydro với Asn22 và Asn31. Các tương tác kỵ nước được hình thành bởi các hợp chất này với dư lượng Arg11, Phe15, Asn21, Ala25 được phát hiện là rất cần thiết cho sự ổn định của phức hợp protein phối tử.

1. INTRODUCTION

Diabetes of type 1 and type 2 is a serious disease with an increasing incidence among young people. According to a report by the International Diabetes Federation, it is estimated that 463 million people have the disease, accounting for 9.3% of the global adult population (20-79 years). There will be 578 million people infected with the disease (10.2%) in 2030 and 700 million (10.9%) in 2045 (Saeedi et al., 2019). The cost of diabetes treatment and prevention amounted to 376 billion USD in 2010 and is expected to increase to 490 billion USD by 2030 (Zhang et al., 2010). According to studies, type 2 diabetes mellitus accounts for around 90% of all cases of diabetes. Type 2 diabetes is characterized by (i) insulin-producing β cells of pancreatic islets are unable to produce and/or insufficient secretion of insulin, (ii) impaired peripheral insulin, and (iii) aggregation of human islet amyloid polypeptide (hIAPP) (DeFronzo et al., 2015), (Bhowmick et al., 2022), (Zraika et al., 2010). In fact, hIAPP is a small peptide hormone 37 amino acids long that plays a physiological role in glucose regulation. The aggregation of hIAPP contributes to the onset of type 2 diabetes (Tran, Ha-Duong, 2016). Numerous studies search the potential pathway inhibiting the aggregation for hIAPP to prevent the development of diabetes mellitus (Brender et al., 2012), (Patel et al., 2014).

Currently, there are several classes of orally available pharmacological agents to treat type 2 diabetes: meglitinide, sulfonylurea, glitazones, and dipeptidyl peptidase-IV (DPP4). In addition, some natural polyphenol compounds such as Epigallocatechin 3-Gallate (EGCG), turmeric, resveratrol, and chrysin have been shown to inhibit hIAPP aggregation (Franko et al., 2018), (Mahboob et al., 2022), (Wang et al., 2022). Also, Morin hydrate (2’, 2, 4’, 5, 7-

Pentahydroxyflavone) is another good example of a small molecule compound that has been shown to inhibit amyloid formation by IAPP and to disaggregate already assembled IAPP amyloid fibers (Pithadia et al., 2016). Not surprisingly, one of these natural compounds was found through a process of virtual design and screening (*in silico*) (Alkahtane et al., 2021). Normally, developing one new drug medicine from initial discovery to regulatory approval to market costs about 800 million USD and takes 10-15 years (Dickson, Gagnon, 2004). On the one hand, computing *in silico* accelerates drug discovery, reducing the problems of time scale and cost (Tran et al., 2022; Trung et al., 2023). On the other hand, there is an increased success rate when removing ineffective, toxic compounds before conducting an experimental evaluation.

The tropical climate of Vietnam makes it one of the largest biodiversity-rich regions in the world (Trinh et al., 2016), with represents about 57% of the global plant families, 15% of plant genera, and 4% of plant species (Tran et al., 2021). It is a promising source of new drug candidates for the prevention and treatment of diabetes. In the present study, virtual screening of Vietnamese plant-natural to treat diabetes mellitus. These results can be used for future evaluation by *in vitro* screening method of potential drug candidates.

2. METHODOLOGY

2.1 Protein and ligands preparation

The crystallographic structure of hIAPP1–37 was downloaded from Protein Data Bank (PDB ID 2L86) (Nanga et al., 2011). The ligands set contains 342 compounds derived from Vietnamese herbs, and their chemical structures were taken from the Pubchem and Chemspider database (Ngo, Li, 2013). The structures of the chemical compounds were converted to PDBqt (Protein Data Bank in format qt) with the program Autodock Tools, considering all the ligand bonds as flexible and the protein was set in rigid form (Tran et al., 2011; Trott, Olson, 2010).

2.2 Virtual screening by molecular docking

Molecular docking of 342 Vietherb compounds on hIAPP1–37 was performed by AutoDock Vina 1.1.2 (Trott, Olson, 2010). The center of grid box was determined based on the active site of hIAPP1–37. The grid box was generated to cover entire the hIAPP1–37, and the box size with size_x = 50, size_y = 50, size_z = 50. The docking global search parameter exhaustiveness was set at the default value. The docking results were ordered according to the docking score in kcal/mol. The molecular interactions of top binding compounds and hIAPP1–37 were visualized by Ligplot 2.2.8.

3. FINDINGS AND DISCUSSION

3.1 Top-leads revealed by docking results

The docking scores of top 10 binding compounds are provided in Table 1. Generally, the natural compounds have high binding affinity to hIAPP1–37 (from -9.4 to -8.5 kcal/mol). After virtual screening, five candidates that had good interactions with 2L86 peptide were selected for subsequent analyses.

Table 1. The binding affinity of top 10 compounds ranking by docking scores (kcal/mol).

Compound	Herbs'name	Binding affinity with 2L86
Solasodine	Solanum xanthocarpum schrad	-9.4
Diosgenin	Schizocapsa plantaginea hance	-9.2
Sarsasapogenin	Smilax glabra	-9.1
Peiminine	Fritillaria roylei	-8.9
Hecogenin	Agave americana Lin.	-8.7
Dracorubin	Calamus draco willd	-8.6
Hinokiflavone	Thuja orientalis L.	-8.6
Tanshinon II	Salvia multiorrhiza	-8.6
Tanshinone	Salvia multiorrhiza	-8.5
Isoconessimine	Holarrhena antidysenteria wall	-8.5

In details, the docking results show that five top binding candidates with the strongest binding affinity are Solasodine (-9.4 kcal/mol), Diosgenin (-9.2 kcal/mol), Sarsasapogenin (-9.1 kcal/mol), Peiminine (-8.9 kcal/mol) and Hecogenin (-8.7 kcal/mol).

3.2 Molecular interactions

The binding sites were highly sensitive to the targets. The binding sites of the top five binding compounds are presented in Figure 1. In details, it was observed that Solasodine forms the hydrogen bond with the amino acids Arg11, Hecogenin also creates the hydrogen bond with Asn31, meanwhile Peiminine had two hydrogen bonds with Asn22 and Asn31. Hydrophobic interactions formed by these compounds with residues Arg11, Phe15, Asn21, Ala25 were found to be essential for the stability of the ligand–protein complex (Figure 2). Further analysis of root-mean-square deviation (RSMD) of the binding complex protein-ligand can be refined by molecular simulations.

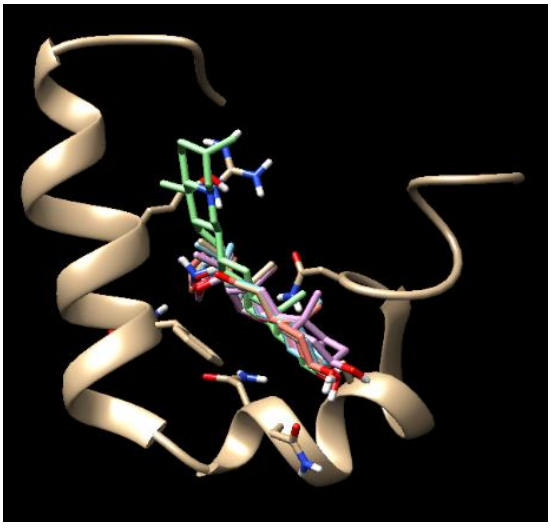

Figure 1. Binding site of top five compounds into hIAPP1–37.

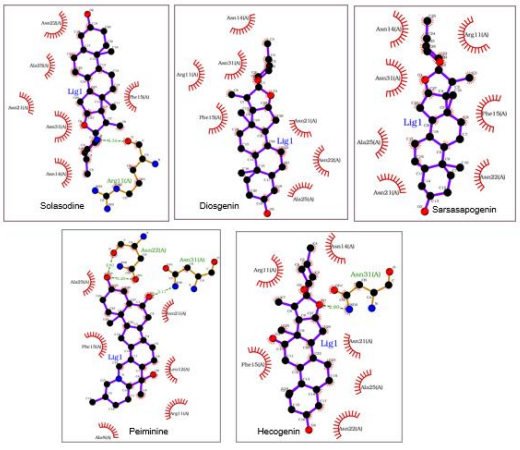

Figure 2. Interaction residues of five top-leads compounds (Solasodine, Diosgenin, Sarsasapogenin, Peiminine and Hecogenin) into the binding site of hIAPP1–37.

4. CONCLUSION

In our work, five inhibitors, namely, Solasodine, Diosgenin, Sarsasapogenin, Peiminine and Hecogenin were identified to have potential inhibitory activities against type 2 diabetes. A set of possible top hits binding interactions between hIAPP1–37 and Vietnamese natural compounds could substantially contribute to the rational drug development against type 2 diabetes. The cell toxicity and solubility need to be assessed in future studies.

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