THE POTENTIAL INHIBITON AGAINST ENZYMES TARGET TYPE 2 DIABETES'S PATHWAYS OF LEONURISIDE VIA VIRTUAL STUDIES

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ABSTRACT

Leonuriside (LN) is a natural compound previously purified from Euonymus laxiflorus Champ. and was found as a novel inhibitor of enzyme-targeting type 2 diabetes (T2D) treatment in our early reports via in vitro tests. This study aims to further characterize LN as a potential inhibitor of α-glucosidase and α-amylase and its high possibility of being developed as an antidiabetic drug via in silico studies. The result of the docking study indicated that LN could bind to targeting enzymes α-glucosidase (Q6P7A9) and α-amylase (1SMD) via forming stable complexes with acceptable root mean square deviation (RMSD) values (< 2.0Å) and good binding energy with low docking score (DS) values of -11.3 and -11.9 kcal/mol, respectively. The drug-likeness, and ADMET properties of LN were further investigated. The drug-likeness properties of LN were further investigated. The data of Lipinski's rule of five analysis and absorption, distribution, metabolism, excretion and toxicity (ADMET)-based pharmacokinetics and pharmacology revealed that LN possesses all the properties fitting the requirement of Lipkin's Rules and good ADMET properties in the required allotted limitation. The results obtained in this work suggested LN is a potential inhibitor of α-glucosidase and α-amylase and may be developed as a T2D drug.

Keywords: *Type 2 diabetes, Leonuriside, Euonymus laxiflorus Champ., α-glucosidase, α-amylase, in silico.*

1. INTRODUCTION

Type-2 diabetes (T2D), a chronic metabolic disorder significantly reduces people's life quality worldwide (Sato K. et al., 2019). The use of α-amylase inhibitors (aAIs) and α-glucosidase inhibitors (aGIs) has been recognized as one of the effective therapies for the management of T2D (DeMelo E.B. et al., 2006; Nguyen T.H. et al., 2022). Up till now, some commercial inhibitors such as acarbose, voglibose, and miglitol have been available for use. However, side effects were found in type 2 diabetes patients when utilizing the therapy with the above inhibitors (Nguyen V.B. et al., 2017a), as such, searching for new and natural enzyme inhibitors for T2D management still is an important task in research.

Enzyme inhibitors including aAIs and aGIs may be obtained from some major sources such as microbes, chemical synthesis, and medicinal plants (Ghani U., 2015; Nguyen V.B. et al., 2018a; Dirir A.M. et al., 2021). Among these, the extracts from medicinal plants have been considered as potential and natural sources for obtaining aAIs and aGIs (Ghani U., 2015; Dirir A.M. et al., 2021). Thus, the studies concerned with screening and identifying active inhibitors from herbal extracts received much interest worldwide.

Euonymus laxiflorus Champ. (ELC) is a medicinal plant distributed in several Asian countries such as Vietnam, China, Myanmar, Cambodia, and India (Nguyen V.B. et al., 2018b). These herbal extracts were reported to show anti-xanthine oxidase and reduced serum uric acid levels in rats (Liu L.M. et al., 2016), antioxidant, anti-NO, prebiotic, and anticancer effects (Nguyen V.B. et al., 2018b; Nguyen Q.V. et al., 2017). In our earlier works, this herbal was also screened as a potential source of aAIs (Nguyen, V.B. et al., 2017b) and aGIs (Nguyen, V.B. et al., 2017c). Of the purified compounds from ELC, the bioactive compound LN was found as novel aAIs and aGI (Nguyen V.B. et al., 2018c; Nguyen V.B. et al., 2018d). However, the basic drug properties as well as the binding energy of this compound toward the targeting enzymes are unknown. In this study, we investigate the interaction and binding energy of LN towards targeting enzymes Q6P7A9 and α-1SMD. The drug-likeness properties of LN were also investigated via the virtual study.

2. STUDY CONTENTS, MATERIALS AND METHODS

2.1. Study contents

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Potential enzymes inhibitory effect of LN via docking study.

The frontier molecular orbitals of LN.

The drug-likeness and ADMET Properties LN.

2.2. Methodologys

2.2.1. Docking study protocol

Docking study was performed following several typical steps mentioned in the previous works (Nguyen T.H. et al., 2022; Nguyen, V.B. et al., 2023).

- *Preparing enzyme structures:* The data structures of enzymes Q6P7A9 and 1SMD were obtained from the Worldwide Protein Data Bank. The 3-D structures of these enzymes were prepared using MOE-2015.10 software and the binding sites on enzymes were found using the function of site finder in MOE. The pH is 7.0 for preparing enzyme structures.

- *Preparing ligand structures:* the 3D structures of ligands LN and acarbose (AC) were prepared and optimized using ChemBioOffice 2018 software and MOE software, respectively.

- *Performance and the output data of docking:* The ligands LN and AC were docked into the binding sites on enzymes Q6P7A9 and 1SMD using MOE. The docking score (DS), the root mean square deviation (RMSD), linkage types, amino acid compositions, and the linkage distances were harvested for analysis.

2.2.2. The Lipkin's Rules of Five analysis

The properties of drug-likeness of the compounds were investigated by Lipkin's Rules of Five performance using the online software which is available for access at (http://www.scfbioiitd.res.in/software/drugdesign/lipinski.jsp).

3. RESULT AND DISCUSSION

3.1. Potential enzymes inhibitory effect of Leonuriside via docking study

When docking a ligand (inhibitor) into its targeting protein (enzyme), the ligand may interact with the enzyme at various sites on the enzyme (named binding sites, BSs). Thus, only the most stable intermolecular structure was selected for further investigation (Gligorić E. et al., 2019). Using the site finder function of MOE, the most active BSs on enzyme Q6P7A9 (Figure 1a) and 1SMD (Figure 1b). The BS on enzyme Q6P7A9 contained 59 amino acids with some residues, including Phe362, Met363, Arg594, Pro595, Arg608, His714, His717, Val718, Phe859, Asp861, Ser865, Leu866, Gly867, Val868, Leu869, and Glu870. The BS on 1SMD enzyme was also found containing 59 amino acids with some residues as below: Arg267, Asn301, Gln302, Arg303, Gly304, His305, Gly309, Ala310, Ser311, Ile312, Thr314, Trp316, Asp317, Trp344, Arg346, Phe348, Gly351, Lys352, Asp353, and Asp356.

In the virtual study, the values of RMSD and DS have been used as important indicators for determining the successful interaction (RMSD $\leq$ 2.0Å) and effective inhibitory effect (DS ≤ -3.20 kcal/mol) of an inhibitor towards the targeting enzyme (Ding Y. et al., 2016; Chandra B.T.M. et al., 2017).

As presented in Table 1, LN displayed significant interaction with enzymes Q6P7A9 and 1SMD with very low RMSD values of 1.53 and 1.73 Å, respectively. AC, a commercial inhibitor was also previously found interacting with these enzymes with accepted RMSD values of 0.94 and 1.59 Å, respectively (Nguyen, V.B. et al., 2023; Nguyen T.H. et al., 2022). These ligands showed efficient binding energy to enzyme Q6P7A9 and 1SMD with DS values of -11.2 to -11.3 kcal/mol and -11.9 to -12.1 kcal/mol, respectively. These results suggested LN is a potential inhibitor of Q6P7A9 and 1SMD. For an inside understanding of the interaction of LN toward targeting enzymes, the binding of this ligand with Q6P7A9 and 1SMD Rat the binding sites were also recorded and presented in Table 2, Figure 2, and Figure 3.

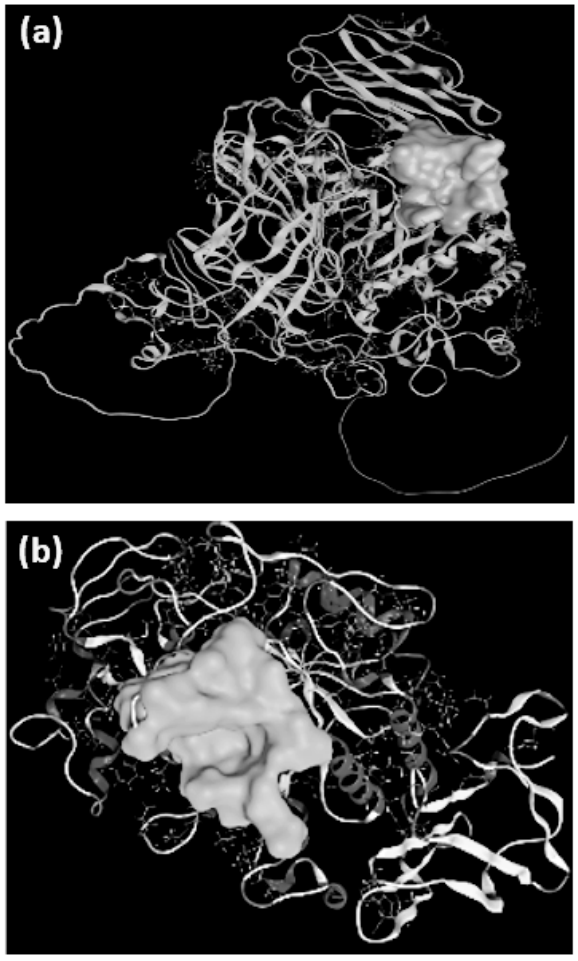

Figure 1. The 3D structures and binding sites of enzymes Q6P7A9 (a) and 1SMD (b)

Table 1. The data of docking study of ligands LN and AC binding with Q6P7A9 and 1SM

Ligand	Enzyme	RMSD (Å)	DS (kcal/mol)	Ref.
LN	Q6P7A9	1.5	-11.3	This study
AC	Q6P7A9	0.94	-11.4	[*]
LN	1SMD	1.7	-11.9	This study
AC	1SMD	1.59	-12.1	[**]

Referenced from the previous reports: Nguyen, V.B. et al., 2023 (*); Nguyen T.H. et al., 2022 (**).

Table 2. The data of linkages, the distance, and energy binding of the interaction between ligands LN and enzymes Q6P7A9 and 1SMD

Complex	Linkages	Amino acids [Distance (Å)/E (kcal/mol)/ linkage type]
LN-Q6P7A9	6 linkages (4H-donor, 2H-acceptor)	His717(3.30/−0.7/H-donor) Glu870(2.78/−3.7/H-donor) Ser865(2.73/-2.2/H-donor) Ser584(2.89/-2.0/H-donor) Gly867(3.25/−1.6/H-acceptor) Val868(2.99/−2.3/H-acceptor)
LN-1SMD	3 linkages (2H-donor, 1pi-H)	Asp317(3.00/−3.2/H-donor) Asn301(2.84/−2.2/H-donor) Phe348(3.59/−0.6/pi-H)

The ligand LN effectively bound to enzyme Q6P7A9 (Figure 2) by interacting with 6 amino acids, including His717, Glu870, Ser865, Ser584, Gly867, and Val868 for creating 6 linkages. Of these, 4 H-donor and 2 H-acceptor linkages were formed (Table 2). This ligand was also found interacting with enzyme 1SMD (Figure 3) at its active zone with good binding energy via connecting with several amino acids (Asp317, Asn301, and Phe348), and 3 linkages were generated. Of those, 2 H-donor linkages were formed via the interaction of LN with Asp317, and Asn301 while 1pi-H was created via the interaction of LN with Phe348 (Table 2). In our previous works, acarbose was also found highly bound to enzymes Q6P7A9 (Nguyen, V.B. et al., 2023) and 1SMD (Nguyen T.H. et al., 2022) via creating 5 linkages (2 H-donor, 3 H-acceptor) and 4 linkages (1 H-donor and 3 H-acceptor), respectively.

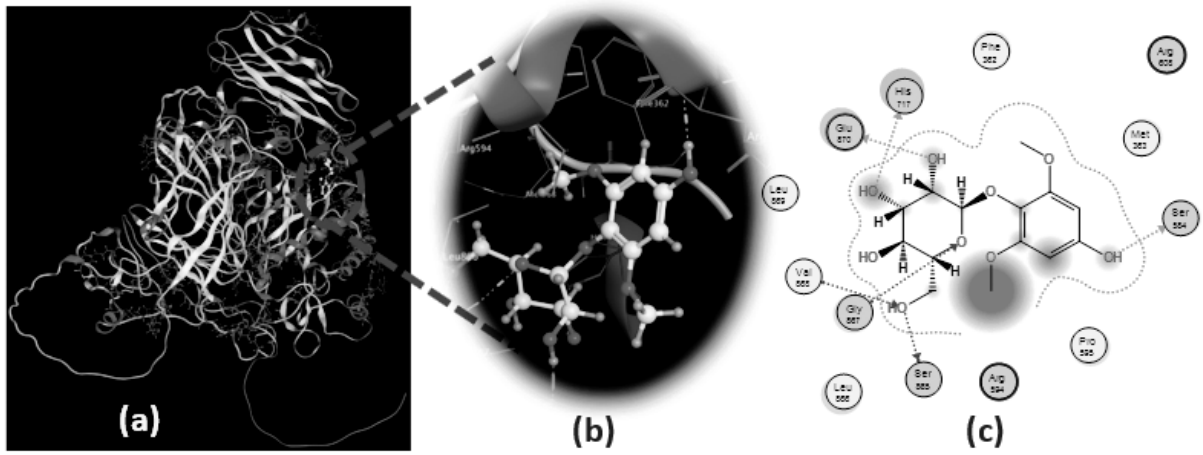

Figure 2. Interaction of ligand LN with enzyme Q6P7A9 (a). The 3D (b) and 2D (c) structures of ligand LN at the active site 1 of Q6P7A9

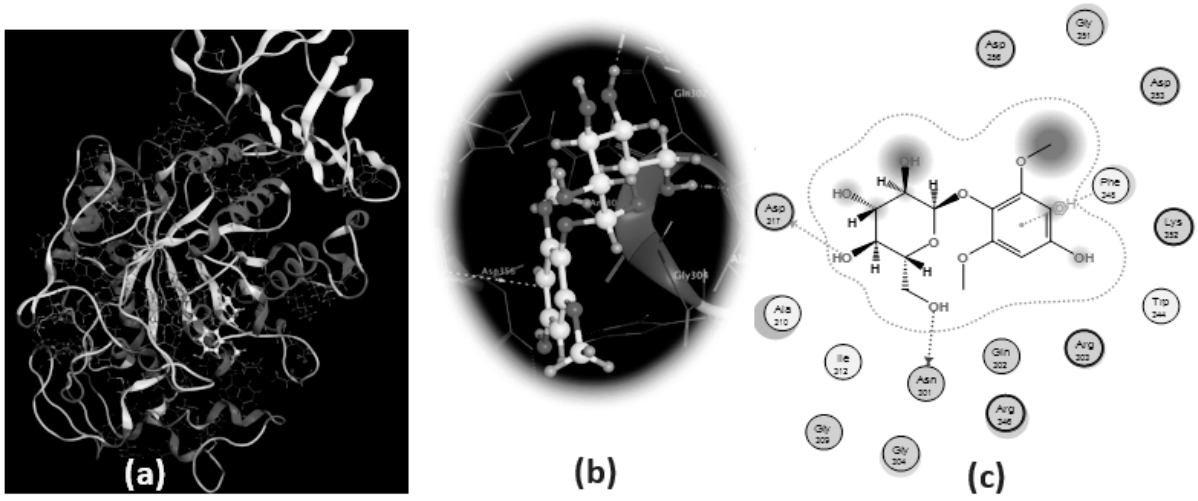

Figure 3. Interaction of ligand LN with enzyme 1SMD (a). The 3D (b) and 2D (c) structures of ligand LN at the active site 1 of 1SMD3.2. The frontier molecular orbitals of Leonuriside

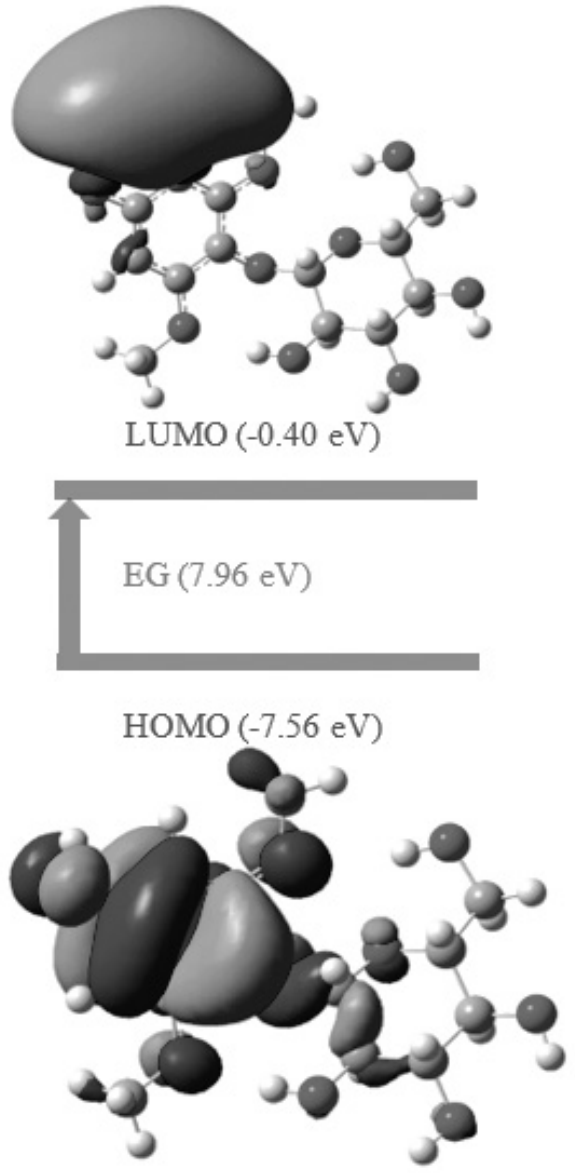

Figure 4. HOMO and LUMO of ligand LN analyzed by DFT at level of theory b3lyp/6-311++g(d,p)

The frontier molecular orbitals of LN were further examined. The highest occupied molecular orbital data (HOMO) and lowest unoccupied molecular orbital data (LUMO) of this ligand were illustrated and presented in Figure 4. The structure of LN displayed its low E_{HOMO} value of -7.56 eV, showing its electronic stability is high (accepted < −5 eV) (Loan H.T.P. et al. 2020). It has been evidenced that a ligand shows effective capability of intermolecular binding toward protein structures when its molecular structure has an energy gap (EG) value of insulation to semiconduction (3.2eV<EG<9eV) (Rosenberg B. 1962). In this study, the molecular structure of LN was investigated with the energy gap value of 7.96 eV, indicating it has potential intermolecular binding capability toward the targeting enzyme.

3.3. The drug-likeness and ADMET Properties of Leonuriside via Lipkin's Rules of Five

To investigate the potential of LN in drug development, Lipki's rules of Five and ADMET Properties were explored and the data were summarized in Table 3 and 4, respectively.

Lipki's rules of Five have been commonly applied for evaluating the drug-likeness of drug candidate compounds (Kim Y. et al., 2004; Nguyen, V.B. et al., 2023). Lipki's rules of Five include "molecular mass <500 Da, high lipophilicity with LogP value <5), number of H-donors <5, number of H-acceptors <10, and the molar refractivity in the range of 40-130". A compound satisfying ≥2 rules may be suggested as having properties of drug-likeness. Lipkin's rules of Five data of LN and AC were investigated. As shown in Table 3, LN may satisfy all the properties fitting the requirement of Lipki's rules of Five, indicating this compound has good drug-likeness properties, as such it has a

high possibility of being used as a potential drug. Acarbose was analyzed for comparison and this commercial inhibitor only satisfied approximately 2 rules.

Table 3. The Lipkin's Rules of Five of LN and AC

Rules	Ligands		Lipki's rules
	LN	AC	
Mass (Da)	332	646	< 500
H-donor	5	15	< 5
H-acceptors	9	18	< 10
LogP	-1.88	-9.59	< 5
Molar Refractivity	75.6	136.5	40-130

The ADMET properties of LN and AC were explored (Table 4). Regarding the absorption property, LN played howed a high level of intestinal absorption (human) values in the range of 34.57%, while AC showed a very poor ability of absorption of 4.172 %. In terms of drug distribution, the log VDss value of LN was found at -0.047 log $L.kg^{-1}$, indicating that this inhibitor compound showed a plasma-tissue balance (-0.15<logVDss<0.45). AC showed a low VDss value of -0.836, indicating Its preference for blood plasma over tissue (Sarukhanyan E. et al., 2022). Both these inhibitors (LN and AC) may not cross the blood–brain barrier (BBB) since their BBB permeability values were low (logBB < − 1). Concerning metabolism, LN and ABC found no effects on the substrates and inhibitors of the cytochromes P450 family, indicating that these compounds may not be oxidized in the liver and may be stable in the living system [20]. Regarding the property of excretion, the prediction that LN and AC may be carried out via the Organic Cation Transporter 2 due to having total clearance values of 0.72 and 0.428 log $mL.min^{-1}.kg^{-1}$, respectively [12]. Notably, both LN and AC demonstrated no AMES toxicity. Overall, LN displayed good ADMET properties in the required allotted limitation.

Table 4. The ADMET properties of LN and AC

Compd / Property	LN	AC	Unit
Absorption			
Water solubility	-2.203	-1.482	(1)
Caco2 permeability	-0.195	-0.481	(2)
Intestinal-absorption	34.57	4.172	(3)
Skin-permeability	-2.741	-2.735	(4)
P-glycoprotein substrate	Yes	Yes	(5)
P-glycoprotein I inhibitor	No	No	(5)
P-glycoprotein II inhibitor	No	No	(5)
Distribution			
VDss	-0.047	-0.836	(6)
Fraction-unbound	0.509	0.505	(6)
BBB permeability	-1.375	-1.717	(7)
CNS permeability	-4.673	-6.438	(8)
Metabolism			
CYP2D6 substrate	No	No	(5)
CYP3A4 substrate	No	No	(5)
CYP1A2 inhibitor	No	No	(5)
CYP2C19 inhibitor	No	No	(5)
CYP2C9 inhibitor	No	No	(5)
CYP2D6 inhibitor	No	No	(5)

Compd / Property	LN	AC	Unit
CYP3A4 inhibitor	No	No	(5)
Excretion			
Total Clearance	0.72	0.428	(9)
Renal OCT2 substrate	No	No	(5)
Toxicity			
AMES toxicity	No	No	(5)
Max. tolerated dose	0.402	0.435	(10)
hERG I inhibitor	No	No	(5)
hERG II inhibitor	No	Yes	(5)
Oral Rat Acute-toxicity (LD50)	2.787	2.449	(11)
Oral Rat Chronic Toxicity	4.367	5.319	(12)
Hepatotoxicity	No	No	(5)
Skin Sensitization	No	No	(5)
T.Pyriformis toxicity	0.285	0.285	(13)
Minnow-toxicity	3.719	16.823	(14)

Note: (1) log mol·L−1; (2) log Papp (10−6 cm·s−1); (3) %; (4) log Kp; (5) Yes/No; (6) log L·kg−1; (7) log BB; (8) log PS; (9) log mL·min−1·kg−1; (10) log mg·kg−1·day−1; (11) mol·kg−1; (12) log mg·kg−1_bw·day−1; (13) log μg·L−1; (14) log mM.

4. CONCLUSIONS

LN was characterized as a potential antidiabetic compound via virtual studies in this study. LN was found highly binding to enzymes Q6P7A9 and α-1SMD associating with type 2 diabetes with acceptable RMSD value (≤ 2.0Å) and good DS values of -11.3 and -11.9 kcal/mol, respectively. These energy binding of LN are comparable to those of acarbose, an antidiabetic compound with DS values of -11.2 to -12.7 kcal/mol, respectively. Furthermore, based on Lipkin's Rules of Five analysis, this compound demonstrated good drug-likeness properties and displayed good ADMET properties in the required allotted limitation, thus, it has a high possibility to be used as a potential drug for the management of type 2 diabetes.

AUTHOR CONTRIBUTION

Conceptualization, resources, writing—original draft preparation, NVB; methodology, software and validation, data curation, visualization, and project administration, writing—review, and editing, NVB., HTTT, and PTHT; formal analysis, HTTT, NTTO, NAD, and N.V.B; investigation, HTTT, NTTO, and T.H.T.P.

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TIỀM NĂNG ỨC CHẾ ENZYME MỤC TIÊU KHÁNG TIỂU ĐƯỜNG TYPE 2 CỦA HỢP CHẤT LEONURISIDE THÔNG QUA NGHIÊN CỨU IN SILICO

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TÓM TẮT

Leonuriside (LN) – một hợp chất tự nhiên đã được cô lập từ Euonymus laxiflorus Champ. và được ghi nhận mới là chất ức chế enzyme tiềm năng liên quan tới bệnh tiểu đường type 2 trong công bố trước của chúng tôi. Mục tiêu của nghiên cứu này là xác định tiềm năng ức chế và khả năng phát triển thuốc kháng tiểu đường của LN thông qua nghiên cứu mô phỏng. Kết quả mô phỏng cho thấy, LN tương tác và tạo phức bền với enzyme α-glucosidase (Q6P7A9) và α-amylase (1SMD) với giá trị RMSD được chấp nhận (< 2.0Å) và năng lượng liên kết tương ứng là 11.3 and -11.9 kcal/mol. Đặc tính thuốc của hợp chất LN cũng được nghiên cứu. Kết quả phân tích 5 nguyên tắc của Lipkin và dược lý dựa trên năm phân tích và hấp thụ, phân phối, chuyển hóa, bài tiết và độc tính (ADMET) của Lipinski cho thấy hoạt chất này đáp ứng đầy đủ cả 5 nguyên tắc của Lipkin và có những đặc tính tốt về dược lý. Những kết quả ghi nhận trong báo cáo này minh chứng và đề nghị hợp chất LN là chất ức chế enzyme tiềm năng và có khả năng phát triển thuốc kháng tiểu đường type 2.

Từ khóa: *Tiểu đường type 2, Leonuriside, Euonymus laxiflorus Champ., α-glucosidase, α-amylase, in silico.*

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