Vietnam Journal of Science and Technology ***62*** *(4) (2024) 648-659*

doi:10.15625/2525-2518/18215

Potential inhibitory activities of phytoconstituents in *Salvia miltiorrhiza* against coronary heart disease drug targets using docking and ADMET studies

Man Thi Thuy Duong[1], Nguyen Ngoc Long[2], Pham Hai Son[3], Tran Thi Hoai Van[4], Long Giang Bach[5, 6], Pham Quoc Long[7], Ha Viet Hai[7], Do Tien Lam[7], Pham Thi Hong Minh[7 ,8], Le Thi Thuy Huong[7,*]

[1]*Faculty of Biology, VNU University of Science, Vietnam National University, 2 Xuan Thuy, Cau Giay, Ha Noi, Viet Nam*

[2]*Faculty of Chemistry and Environment, Thuy Loi University, Ha Noi, Viet Nam*

[3]*Hanoi University of Business and Technology, 29/124 Vinh Tuy, Hai Ba Trung, Ha Noi, Viet Nam*

[4]*Vietnam University of Traditional Medicine, 2 Tran Phu, Ha Dong, Ha Noi, Viet Nam*

[5]*NTT Hi-Tech Institute, Nguyen Tat Thanh University, Ho Chi Minh City, Viet Nam*

[6]*Center of Excellence for Functional Polymers and Nano Engineering, Nguyen Tat Thanh University, Ho Chi Minh City, Viet Nam*

[7]*Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi, Viet Nam*

[8]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi, Viet Nam*

[*]Emails*: thuyhuong0102sp2@gmail.com*

Received: 2 April 2023; Accepted for Publication: 24 February 2024

Abstract. Coronary heart disease (CHD) is one of the leading causes of death worldwide. The effectiveness of the current drugs is still restricted due to high side effects; thus, it is urgently needed to discover novel compounds for drug development. In the field of drug discovery research, the main target receptors for chemotherapy are identified as ACE, PPAR-γ, HMGR, COX-2, and thrombin. In this study, docking simulations were performed for phytoconstituents of *Salvia miltiorrhiza* Bunge in searching for compounds with potential inhibitory activities against these proteins. As a result, six compounds were suggested as potential multitarget inhibitors and could be considered for further drug development studies based on docking conformation and ADMET property analysis.

Keywords: Coronary heart disease, *Salvia miltiorrhiza*, molecular docking, ADMET.

Classification numbers: 1.2.1, 1.2.4

1. INTRODUCTION

Coronary heart disease (CHD) is the single largest cause of death in the developed countries and is one of the leading causes of disease burden in developing countries [1]. In recent decades, although the incidence of CHD has decreased slightly, the disease is still responsible for one third of mortality worldwide and thus remains a burden to the health systems of the nations [2]. Currently, the common treatment for CHD is the use of oral medications or stenting in the blood vessels [3, 4]. The stenting method has not been widely used since it depends on the patient's condition as well as concerns about the safety of this treatment, therefore, the development of oral drugs remains the most effective approach. This method includes searching for bioactive compounds capable of inhibiting multiple receptors to radically treat coronary heart disease. These receptor targets could be enzymes, proteins regulating cellular metabolism, whose activity may lead to factors that increase the risk of coronary heart disease such as blood pressure, contraction vessels, high blood cholesterol, etc. Previous studies have proven the following proteins are common targets for drug development: ACE (Angiotensin-converting enzyme), PPAR-γ (Peroxisome proliferator activated receptor γ), HMGR (Hydroxymethylglutaryl coenzyme-A receptor), COX-2 (Cyclooxygenase-2), and thrombin.

ACE is a dipeptidyl carboxypeptidase that catalyzes the hydrolysis of dipeptides [5]. The best known function of ACE is the generation of angiotensin II, a potent vasoconstrictor [5, 6]. In addition, ACE also affects blood pressure by cleaving bradykinin (BK) thereby eliminating its vasodilator activity [6]. The PPAR-γ protein plays an important role when participating in cellular lipid metabolism. Dysfunctional macrophage PPAR-γ may contribute to accelerated atherogenesis in blood vessels [7, 8]. HMGR is an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, a key factor in the regulation of cholesterol levels in the body [9]. During coronary heart disease drug development research, HMGR was identified as one of the main targets because this protein is directly involved in cholesterol biosynthesis, the main cause of coronary heart disease. Normally, COX-2 is absent from cells or has very low activity. When foreign inflammatory factors such as bacteria, viruses, etc. enter, they stimulate the body to produce cytokines, a marker in the inflammatory process, causing COX-2 to increase in monocytes, macrophages, and cartilage tissues. In addition, COX-2 also causes vasodilation and inhibition of platelets, promoting inflammatory responses [10, 11]. Thrombin is an important enzyme in the hemostasis process because it can perform both coagulation and anticoagulant functions. It is therefore implicated in wound healing, the formation of blood clots, and the pathogenesis of conditions such as atherosclerosis, sepsis, and even cancer [12].

In the recent years, computer aided drug design (CADD) play an important role in the research and development process of pharmaceutical industry which significantly save time and cost for scientists in novel drugs research. In this study, we used computing tools to predict the potential of compounds in Danshen (*Salvia miltiorrhiza* Bunge). Danshen is commonly known as a precious herb in folklore, so it is often used to treat various diseases such as cerebral hemorrhage, edema, malignancy, menstrual irregularities, insomnia, liver disorders, anxiety, miscarriage, and cardiovascular related diseases [13]. The goal of the study is to screen and find potential compounds in Danshen, thereby guiding other studies to develop drugs for coronary heart disease.

2. MATERIALS AND METHODS

2.1. Ligand preparation

A database of 157 compounds from Danshen (*Salvia miltiorrhiza* Bunge) was established (Table S1). These compounds were collected from previously published articles [13 - 18]. Their structures were drawn with Marvinsketch software version 19.27.0 and prepared in 3D using PYMOL version 2.2.2 [19], followed by energy minimization using GabEdit version 2.5.0 [20].

2.2. Protein preparation

The PDB entries chosen for docking studies including ACE (PDB ID: 1UZE) [21], PPAR-γ (PDB ID: 2HFP) [22], HMGR (PDB ID: 1HW8) [23], COX-2 (PDB ID: 1CX2) [24] and thrombin (PDB ID: 1YPJ) [25] were obtained from the Protein Data Bank archive (PDB). All protein models were chosen based on high resolution criteria (less than 2.5 Å). The protein structure was prepared using the Graphical User Interface program named Autodock Tools (ADT).

2.3. Docking using Autodock4

The molecular docking study utilizes AutoDock 4.2.6 with Lamarckian genetic algorithm (LGA) for searching the optimum dock pose together with scoring function to calculate the binding affinity. The AutoDock Tools was employed to set up and perform docking calculation. In this study, we performed the docking study assuming a rigid protein and considered the conformational space of the ligands to analyze the inductive effect of the hybrid compounds. They were utilized to prepare proteins for docking simulations. The heteroatoms, including water molecules, were deleted and polar hydrogen atoms and Kollman charges were added to the receptor molecule. All other bonds were allowed to be rotatable. The binding site was enclosed in a box such that it incorporates the amino acids involved in constituting the active site of targeted proteins. Details of key residues for each protein are presented in Supplement information file. For the ACE, the dimensions in (x × y × z) were 58, 42, 40 with the center coordinates of the box being 40.394, 34.869, 44.617. PPAR-γ had dimensions in (x × y × z) of 62, 70, 56 with box center coordinates of 23.986, -10.506, 2.778. HMGR had dimensions in (x × y × z) of 34, 36, 44 with box center coordinates of 24.734, -16.949, 16.499. COX-2 had dimensions in (x × y × z) of 58, 56, 68 with box center coordinates of 23.164, 21.905, 14.653 and thrombin were 64, 42, 52 (x × y × z) with box center coordinates of 15.345, -12.012, 20.414, with grid spacing of 0.375 Å. The AutoGrid and AutoDock were used to calculate the precomputed binding affinities of each type of ligand atom and to perform simulated molecular binding, respectively. The parameters of the Lamarckian genetic algorithm (LGA) were set as follows: 30 runs; elitism was 1; mutation rate was 0.02; population size was 300; crossover rate was 0.8; number of generation was 27 000; the energy rating was 25 000 000 and the offset (Root Mean square-RMD) was set to 2.0 Å during each run. From the most favored cluster, the ligand conformation for further analysis was selected on the basis of the lowest free binding energy.

2.4. ADMET studies

The online server Molinspiration was utilized for bioactivity prediction (https://www.molinspiration.com) and pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) was used to evaluate drug-like properties. OSIRIS Property Explorer (http://www.organicchemistry.org/prog/peo) was used to predict side effects, such as mutagenic, tumorigenic effects.

2.5. Computing resources and data analysis

All the calculations were done on a single Intel(R) Xeon(R) CPU X5650 @ 2.67 GHz core on a Linux x86_64 cluster. The outputs from AutoDock 4.2.6 were analyzed using PyMOL and Discovery Studio Visualizer (‘‘Dassault Systèmes BIOVIA, Discovery Studio Visualizer, v21.1.0.20298, San Diego: Dassault Systèmes, 2021’’). The PyMOL was used to calculate the distances of hydrogen bonds as measured between the hydrogen and its assumed binding partner. A hydrogen bond (HB) is defined if the angle of an acceptor (A)–hydrogen (H)–donor (D) is larger than 135 with the distance from A to D is smaller than 0.35 nm.

3. RESULTS AND DISCUSSION

3.1. Molecular docking study

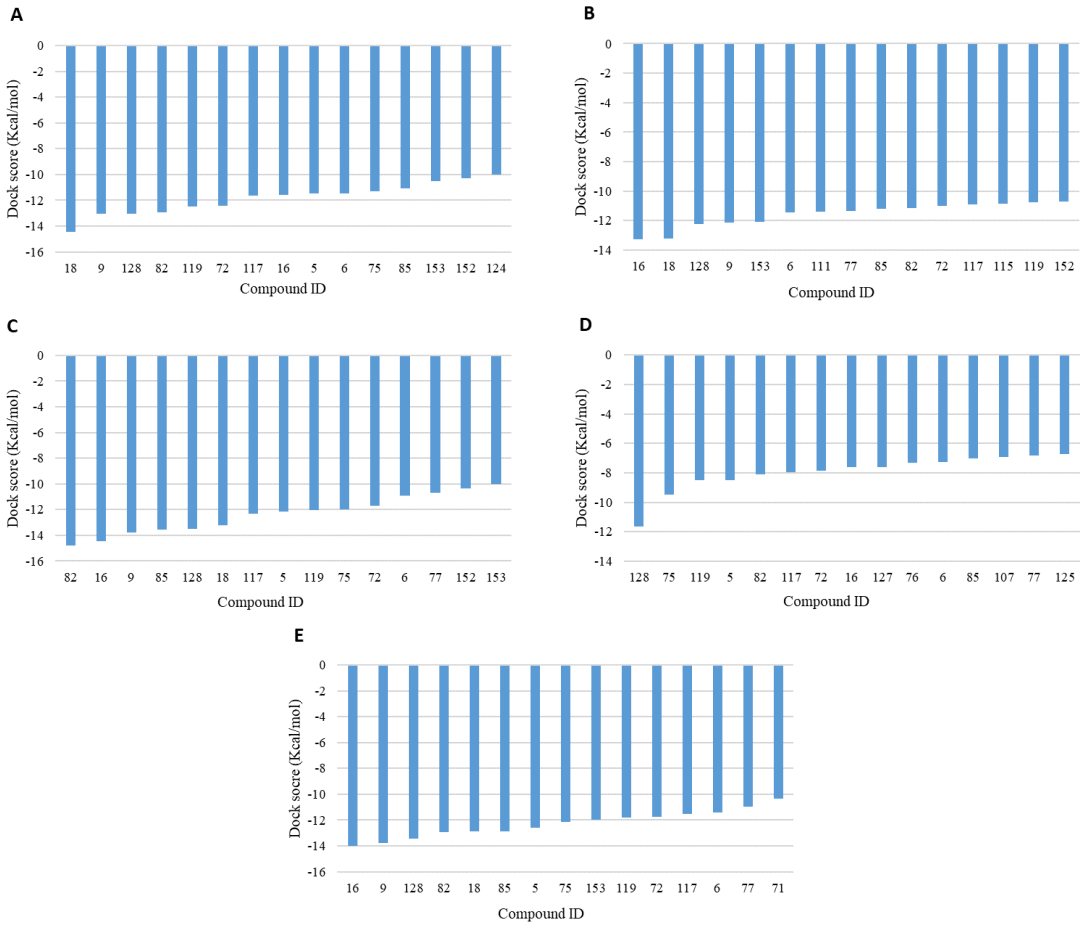


Figure 1. Dock score of top 15 ligands exhibited highest binding affinity toward each targeted proteins. (A) ACE; (B) COX-2; (C) Thrombin; (D) HMGR; (E) PPAR-γ.

In searching for potential inhibitors against drug targets for CHD treatment, AutoDock4 was used to perform docking studies for 157 compounds isolated from Danshen (*Salvia miltiorrhiza* Bunge). In docking simulation, binding free energy (ΔG) is calculated to estimate the binding affinity of the ligand–target complex. According to the criteria of AutoDock4, lower binding free energy values indicate higher stability for the complex and favor the interaction of

ligand within the binding site when predicting the docking pose [26, 27]. Binding free energies of all studied compounds are presented in supplementary file (Table S2). The dock score of the top 15 ligands toward each protein target is presented in Figure 1.

Table 1. Docking results of "hit" compounds against targeted proteins.

ID	Compound name	Ligand efficiency (LE)	Hydrogen bond interacting amino acids
ACE Protein			
Dock6	Rosmarinic acid	-0.44	Gln281, Glu411, Asp453, Lys511, Tyr520
Dock16	Salvianolic acid C	-0.32	Thr282, Ala354, Glu376, His383, Glu411, Lys454
Dock18	Methyl salvianolate C	-0.39	Gln281, Glu384, Tyr520
Dock72	Salvianic acid C	-0.46	Gln281, Asp415, Lys454, Lys511, Tyr520
Dock82	Methyl salvianolic acid C	-0.35	Thr282, Ala354, Glu384
Dock85	Isosalvianolic acid C	-0.31	Ala354, Asp415
Dock117	Salvianolic D	-0.39	Asn277, Gln281, Thr282, Lys511
Dock119	Baicalin	-0.39	Glu162, Lys511, Tyr510, Tyr523
Dock128	Saccharose	-0.57	Asp453, Lys511, Tyr520
PPAR-γ Protein			
Dock6	Rosmarinic acid	-0.44	Lys265, Ile326, Ser342, Glu343
Dock16	Salvianolic acid C	-0.39	Ile326, Ser342, Glu343
Dock18	Methyl salvianolate C	-0.35	Glu259, Lys265, Arg288, Glu343
Dock72	Salvianic acid C	-0.44	Glu259, Ser342
Dock82	Methyl salvianolic acid C	-0.35	Glu259, Lys265, Leu270, Ser342
Dock85	Isosalvianolic acid C	-0.36	Arg288, Glu291, Leu330, Ser342
Dock117	Salvianolic D	-0.38	Glu259, Ile262, Lys265, His266
Dock119	Baicalin	-0.37	Lys2654, Ile281
Dock128	Saccharose	-0.58	Lys265, Arg280, Cys285
HMGR Protein			
Dock6	Rosmarinic acid	-0.28	Ser684, Asn686, Lys691
Dock16	Salvianolic acid C	-0.21	Arg590, Ser684, Asp690, Lys691
Dock18	Methyl salvianolate C	-0.18	Arg590, Ser684, Asn686
Dock72	Salvianic acid C	-0.29	Ser684, Asn686, Asp690, Lys691
Dock82	Methyl salvianolic acid C	-0.22	Arg590, Ser684, Asn686, Cys688, Lys691, Lys692
Dock85	Isosalvianolic acid C	-0.19	Ser684, Asn686, Asp690, Lys691, Lys692
Dock117	Salvianolic D	-0.26	Ser684, Asn686, Lys692
Dock119	Baicalin	-0.27	Ser684, Asp690, Lys691
Dock128	Saccharose	-0.51	Arg590, Asp690, Lys691
COX-2 Protein			
Dock6	Rosmarinic acid	-0.44	Arg120, Tyr385
Dock16	Salvianolic acid C	-0.37	His90, Arg513, Ile517, Phe518, Ala527
Dock18	Methyl salvianolate C	-0.25	Arg120, Gln192
Dock72	Salvianic acid C	-0.41	Arg120, Tyr385
Dock82	Methyl salvianolic acid C	-0.30	Tyr355, Tyr385, Ser530

Dock85	Isosalvianolic acid C	-0.31	His90, Gln192, Leu352, Arg513, Asp515, Phe518
Dock117	Salvianolic D	-0.36	His90, Leu352, Tyr385, Arg513, Ser530
Dock119	Baicalin	-0.34	Gln192
Dock128	Saccharose	-0.53	nil
	Thrombin Protein		
Dock6	Rosmarinic acid	-0.42	His57, Ser195, Gly216, Gly219
Dock16	Salvianolic acid C	-0.40	Lys60, Asn143, Glu146, Ala190, Ser195, Gly216
Dock18	Methyl salvianolate C	-0.35	Asp189, Gly216
Dock72	Salvianic acid C	-0.43	Lys60, Gly216
Dock82	Methyl salvianolic acid C	-0.40	Lys60, Cys191, Ser195, Gly216
Dock85	Isosalvianolic acid C	-0.38	Lys60, Ser214, Trp215, Gly219, Cys220, Phe227
Dock117	Salvianolic D	-0.41	Lys60, Ser195, Gly216
Dock119	Baicalin	-0.38	Cys42, Leu41, Lys60, Glu192
Dock128	Saccharose	-0.59	Gly216, Gly219

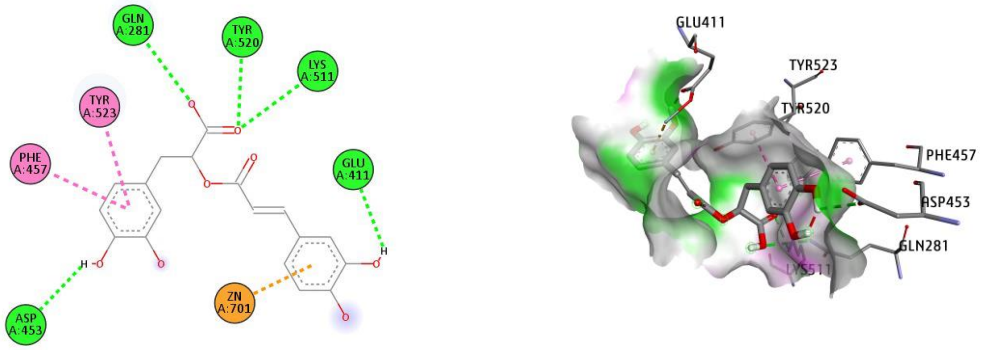
In this study, among investigated molecules, 9 out of 157 compounds were assumed as multiple inhibitors since they are ranked as topmost in most of the targeted protein, including compounds **6**, **16**, **18**, **72**, **82**, **85**, **117**, **119**, and **128** (approximately 5% out of the total studied compounds). In particular, it is observed that these molecules preferentially bind to ACE and Thrombin protein targets than the others based on dock score ranking. Compound **6**, **18**, **72**, and **119** exhibited their highest binding affinity toward ACE protein (-11.47, -14.32, -12.40, and -12.49 kcal/mol) while compound **16**, **82**, **85**, **117** and **128** exhibited their highest binding affinity toward Thrombin protein (-14.47, -14.80, -13.58, -12.30, and -13.48 kcal/mol, respectively). It should be noted that compound **6** (rosmarinic acid) and **119** (baicalin) has been reported to exhibit acetylcholinesterase inhibitory activity through experimental assays [28, 29]. On the other hand, Liu X. *et al.* published their study on antithrombotic mechanism of Salvianolic acids (compound **16** and **117**) in 2018 [30]. Based on these evidences, the top rank compounds could be assumed as "hit" candidates for further analysis. Detailed docking results of "hit" compounds are tabulated in Table 1.

These nine potential compounds were then further analyzed for the ligand efficiency (LE) index and their best binding conformation towards their highest binding affinity protein targets (Table 1). Since ACE and Thrombin proteins are most anchored by potent molecules based on binding affinity ranking. Figure 2 depicts the energetically most favorable docking conformation of "hit" against these receptors. It should be noted that most of the interactions formed between targeted proteins and potential molecules were contributed by residues that participated in constituting the active site of the corresponding protein (Supplement information). These data might shed light on the mechanism of action of these compounds within the binding sites of ACE and Thrombin protein targets.

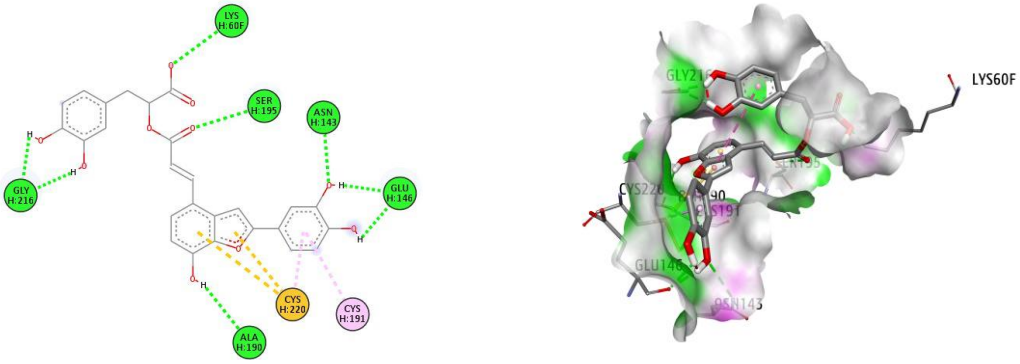
Ligand efficiency (LE) is a measurement for the binding energy of the ligand per atom. This unit is calculated according to the following equation:

$$\Delta g = \frac{\Delta G}{N_{non-hydrogen\,atoms}}$$

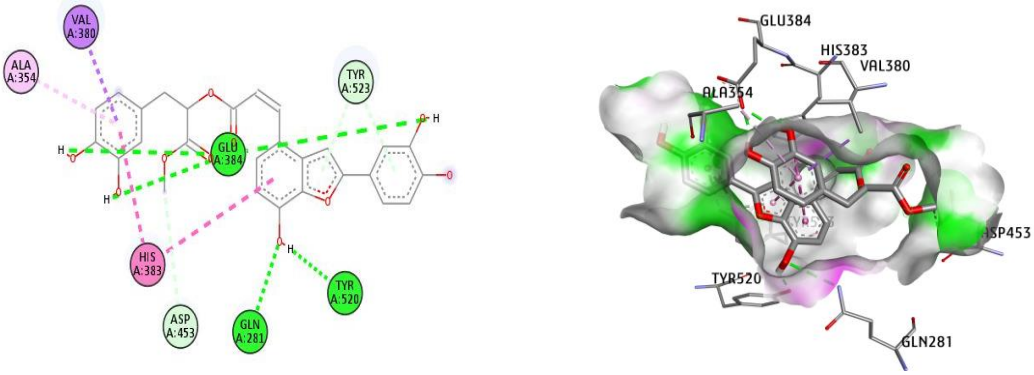
in which, Δg: Ligand efficiency; ΔG: Binding free energy.



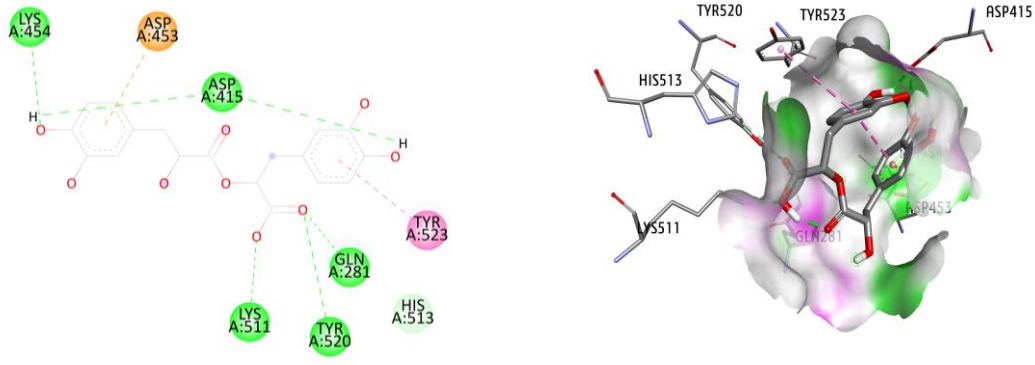
Best docking conformation of compound **6** towards ACE protein.



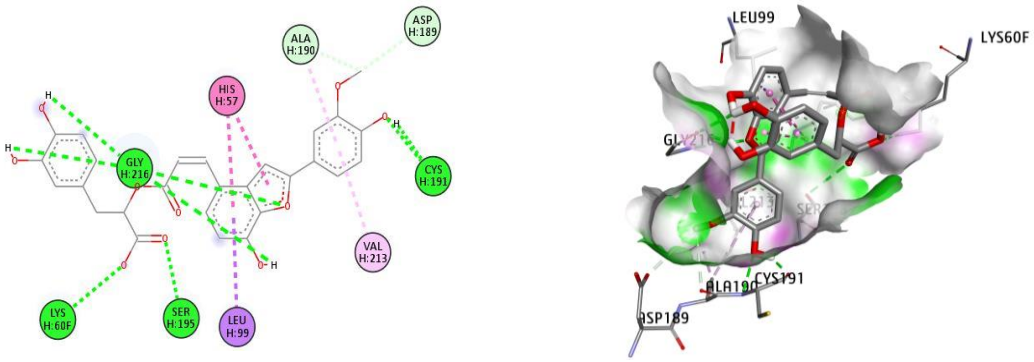
Best docking conformation of compound **16** towards Thrombin protein.



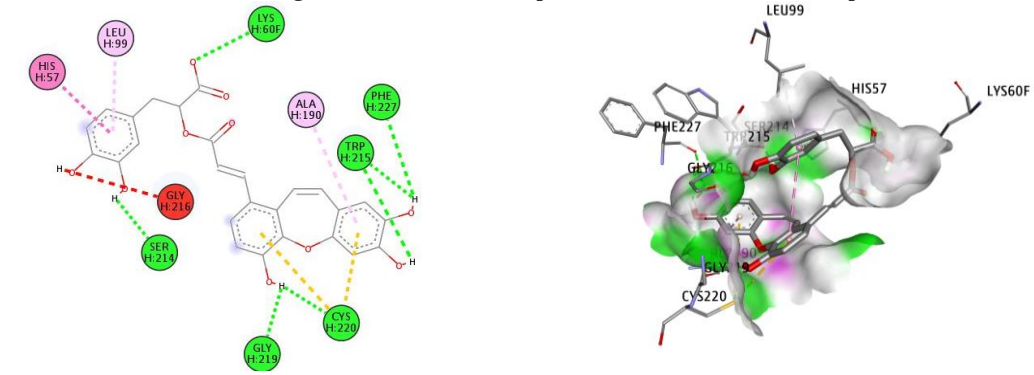
Best docking conformation of compound **18** towards ACE protein.



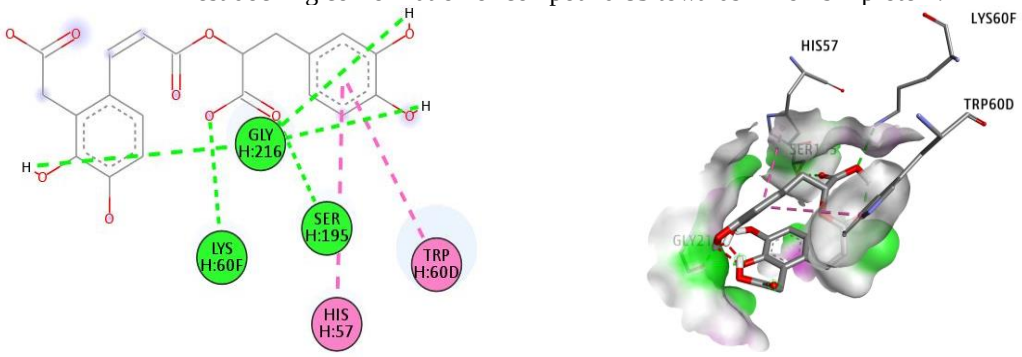
Best docking conformation of compound **72** towards ACE protein.



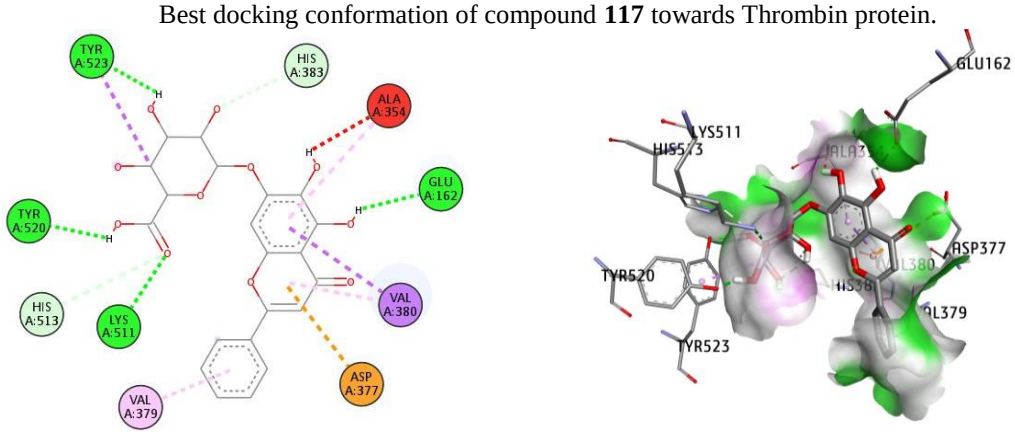
Best docking conformation of compound **82** towards Thrombin protein.



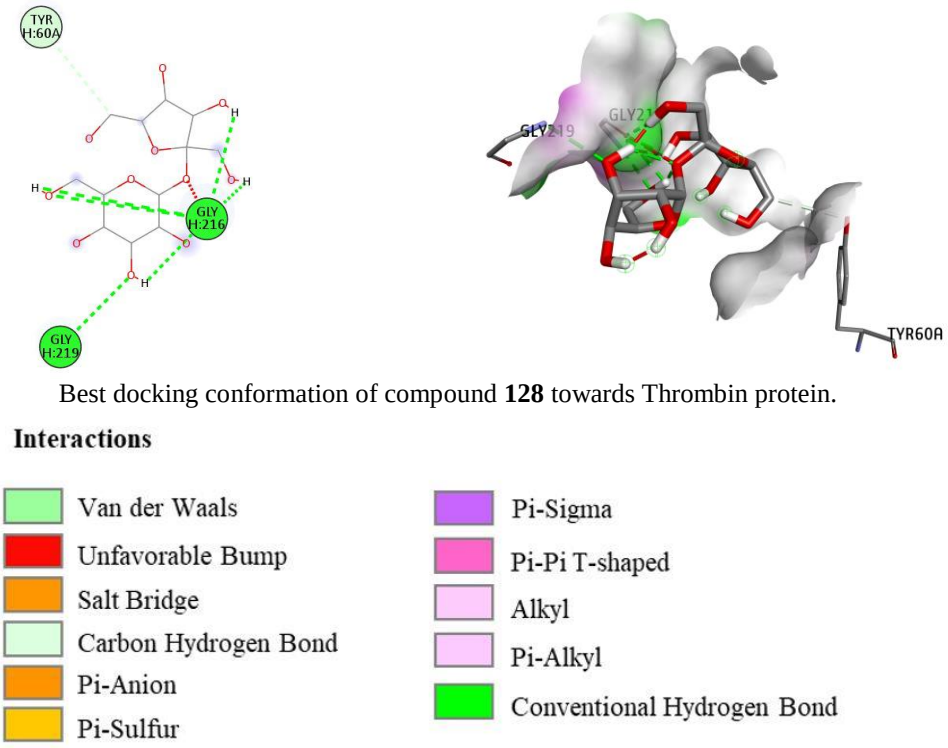
Best docking conformation of compound **85** towards Thrombin protein.



Best docking conformation of compound **117** towards Thrombin protein.



Best docking conformation of compound **119** towards ACE protein.



Best docking conformation of compound **128** towards Thrombin protein.

Figure 2. Binding conformations of potential ligands within the active site of studied proteins suggested by molecular docking simulation.

This parameter is widely used as a useful metric for the selection of potential compounds for further structure optimization during the drug development process. Statistically, if the LE value of compound varies within 0.3 < LE < 0.5 then it could be considered as suitable for further structural modification. According to the obtained data, the LE value of 7 out of 8 potential compounds (except compound **128**) fall within this range, thus, this ligand was excluded from being considered for further drug development steps.

3.2. ADMET studies

The drug-like properties of 157 studied compounds were further assessed by subjecting them to Lipinski's Rule of Five (Ro5) and ADMET properties. Analysis results are reported in Table S3 and Table S4. The Lipinski's Rule of Five consists of criteria that determine which compound is considered to be drug-like in nature, such as molecular weight < 500 Da, number of hydrogen bond donors ≤ 5, number of hydrogen bond acceptors ≤ 10, octanol water partition coefficient (LogP) < 5 and Molar refractivity (MR) from 40 - 130. It is stated that compound violates no more than two criteria might be considered to be potential oral bioavailability. The outcome data indicate that compound 82 should not be considered for future oral drug development since it violates up to 4 criteria. As a result, 7 out of 8 molecules were assumed as favorable for oral drug development.

On the other hand, the research compounds were also evaluated for pharmacokinetic properties and toxicity prediction (Table 2 and Table S4).

Table 2. Pharmacokinetic properties of potential substances.

Compound ID	Name	HIA (% absorbed)	Mutangenic	Tumorigenic
6	Rosmarinic acid	44.39	no	no
16	Salvianolic acid C	50.21	no	no
18	Methyl salvianolate C	77.07	no	no
72	Salvianic acid C	36.83	no	no
82	Methyl salvianolic acid C	52.34	no	no
85	Isosalvianolic acid C	37.04	no	no
117	Salvianolic D	29.13	no	no
119	Baicalin	40.65	no	no

It is stated that an oral drug candidate with an absorbance of less than 30 % is considered to be poorly absorbed. The assessment results showed that compound **117** possess a HIA value of 29.13, thus, this molecule was considered as not appropriated to develop as an oral drug. The rest candidates including compound **6**, **16**, **72**, **82**, **85**, and **119** were suggested as safe since they are predicted to have no mutangenic or tumorigenic properties.

4. CONCLUSIONS

In this study, phytoconstituents of *Salvia miltiorhiza* Bunge were investigated for potential inhibitory activities against five drug targets of coronary heart disease using molecular docking and ADMET studies. Amongst the 157 studied compounds, 6 molecules including compound **6** (rosmarinic acid), compound **16** (salvianolic acid C), compound **72** (salvianic acid C), compound **82** (methyl salvianolic acid C), compound **85** (isosalvianolic acid C), and compound **119** (baicalin) were identified as potential candidates for further drug development stages based on their multiple inhibitory activities against ACE and Thrombin protein targets. These results might contribute helpful information for developing novel agents used in the treatment of CHD.

Acknowledgement. This research is funded by Project numbered NCVCC 07.01/22-23.

CRediT authorship contribution statement. Man Thi Thuy Duong, Nguyen Ngoc Long: Acquisition of data, Analysis and/or interpretation of data. Pham Hai Son: Acquisition of data, Analysis and/or interpretation of data. Tran Thi Hoai Van, Long Giang Bach: Acquisition of data, Writing - review & editing. Ha Viet Hai, Pham Thi Hong Minh, Do Tien Lam: Writing – original draft, Analysis and/or interpretation of data, Writing - review & editing. Pham Quoc Long, Le Thi Thuy Huong: Conception and design of study, Writing – review & editing, Supervision.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Gaziano T. A., Bitton A., Anand S., Abrahams-Gessel S., and Murphy A. - Growing Epidemic of Coronary Heart Disease in Low- and Middle-Income Countries, Curr. Probl. Cardiol. **35** (2) (2010) 72-115. https://doi.org/10.1016/j.cpcardiol.2009.10.002.

2. Sanchis-Gomar F., Perez-Quilis C., Leischik R., and Lucia A. - Epidemiology of coronary heart disease and acute coronary syndrome, Ann. Transl. Med. **4** (13) (2016) 256-256. https://doi.org/10.21037/atm.2016.06.33.
3. Kandaswamy E. and Zuo L. - Recent Advances in Treatment of Coronary Artery Disease: Role of Science and Technology, Int. J. Mol. Sci. **19** (2) (2018) 424. https://doi.org/10.3390/ijms19020424.
4. Elisaf M. - The Treatment of Coronary Heart Disease: An Update, Curr. Med. Res. Opin. **17** (1) (2008) 18-26. https://doi.org/10.1185/0300799039117021.
5. Le D., Brown L., Malik K., and Murakami S. - Two Opposing Functions of Angiotensin-Converting Enzyme (ACE) That Links Hypertension, Dementia, and Aging, Int. J. Mol. Sci. **22** (24) (2021) 13178. https://doi.org/10.3390/ijms222413178.
6. Acharya K. R., Sturrock E. D., Riordan J. F., and Ehlers M. R. W. - Ace revisited: A new target for structure-based drug design, Nat. Rev. Drug Discov. **2** (11) (2003) 891-902. https://doi.org/10.1038/nrd1227.
7. Robbins G. T. - PPAR gamma, bioactive lipids, and cancer progression, Front. Biosci. **17** (1) (2012) 1816–1834. https://doi.org/10.2741/4021.
8. Semple R. K. - PPAR and human metabolic disease, J. Clin. Invest. **116** (3) (2006) 581-589. https://doi.org/10.1172/jci28003.
9. Ojha S., Islam B., Charu C., Adem A., and Aburawi E. - Insight into the mechanism of polyphenols on the activity of HMGR by molecular docking, Drug Des. Devel. Ther. (2015). https://doi.org/10.2147/dddt.S86705.
10. Chan P. C., Liao M. T., and Hsieh P. S. - The Dualistic Effect of COX-2-Mediated Signaling in Obesity and Insulin Resistance, Int. J. Mol. Sci. **20** (13) (2019) 3115. https://doi.org/10.3390/ijms20133115.
11. Zarghi A. and Arfaei S. - Selective COX-2 Inhibitors: A Review of Their Structure-Activity Relationships, Iran J. Pharm. Res. **10** (4) (2011) 655-683.
12. Di Cera E. - Thrombin, Mol. Aspects Med. **29** (4) (2008) 203-254. https://doi.org/10.1016/j.mam.2008.01.001.
13. Wang L., Ma R., Liu C., Liu H., Zhu R., Guo S., Tang M., Li Y., Niu J., Fu M., Gao S., and Zhang D. - Salvia miltiorrhiza: A Potential Red Light to the Development of Cardiovascular Diseases, Curr. Pharm. Des. **23** (7) (2017) 1077-1097. https://doi.org/10.2174/1381612822666161010105242.
14. Kang D. G., Oh H., Sohn E. J., Hur T. Y., Lee K. C., Kim K. J., Kim T. Y., and Lee H. S. - Lithospermic acid B isolated from Salvia miltiorrhiza ameliorates ischemia/reperfusion-induced renal injury in rats, Life Sci. **75** (15) (2004) 1801-1816. https://doi.org/10.1016/j.lfs.2004.02.034.
15. Sun Y., Zhu H., Wang J., Liu Z., and Bi J. - Isolation and purification of salvianolic acid A and salvianolic acid B from Salvia miltiorrhiza by high-speed counter-current chromatography and comparison of their antioxidant activity, J. Chromatogr. B **877** (8-9) (2009) 733-737. https://doi.org/10.1016/j.jchromb.2009.02.013.
16. Su C. Y., Ming Q. L., Rahman K., Han T., and Qin L. P. - Salvia miltiorrhiza: Traditional medicinal uses, chemistry, and pharmacology, Chin. J. Nat. Med. **13** (3) (2015) 163-182. https://doi.org/10.1016/s1875-5364(15)30002-9.
17. Honda G., Koezuka Y., and Tabata M. - Isolation of an antidermatophytic substance from the root of Salvia miltiorrhiza, Chem. Pharm. Bull. (Tokyo) **36** (1) (1988) 408-411. https://doi.org/10.1248/cpb.36.408.

18. Lu P., Nwafor E., Li J., Zhang Q., Qi D., Liu Z., Peng H., Qin H., Gao Y., and Wang J. - Traditional Chinese medicine of Salvia miltiorrhiza Bunge: a review of phytochemistry, pharmacology and pharmacokinetics, Tradit. Med. Res. **6** (4) (2021) 35. https://doi.org/10.53388/tmr20201027204.
19. The PyMOL Molecular Graphics System, Version 2.4.0, Schrodinger, LLC.
20. Allouche A. R. - Gabedit-A graphical user interface for computational chemistry softwares, J. Comput. Chem. **32** (1) (2011) 174-182. https://doi.org/10.1002/jcc.21600.
21. Natesh R., Schwager S. L. U., Evans H. R., Sturrock E. D., and Acharya K. R. - Structural Details on the Binding of Antihypertensive Drugs Captopril and Enalaprilat to Human Testicular Angiotensin I-Converting Enzyme, Biochemistry **43** (27) (2004) 8718-8724. https://doi.org/10.1021/bi049480n.
22. Hopkins C. R., O'Neil S. V., Laufersweiler M. C., Wang Y., Pokross M., Mekel M., Evdokimov A., Walter R., Kontoyianni M., Petrey M. E., Sabatakos G., Roesgen J. T., Richardson E. and Demuth T. P. - Design and synthesis of novel N-sulfonyl-2-indole carboxamides as potent PPAR-γ binding agents with potential application to the treatment of osteoporosis, Bioorg. Med. Chem. Lett. **16** (21) (2006) 5659-5663. https://doi.org/10.1016/j.bmcl.2006.08.003.
23. Istvan E. S. and Deisenhofer J. - Structural Mechanism for Statin Inhibition of HMG-CoA Reductase, Science **292** (5519) (2001) 1160-1164. https://doi.org/10.1126/science.1059344.
24. Kurumbail R. G., Stevens A. M., Gierse J. K., McDonald J. J., Stegeman R. A., Pak J. Y., Gildehaus D., iyashiro J. M., Penning T. D., Seibert K., Isakson P. C., and Stallings W. C. - Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents, Nature **384** (6610) (1996) 644-648. https://doi.org/10.1038/384644a0.
25. Fokkens J. and Klebe G. - A Simple Protocol To Estimate Differences in Protein Binding Affinity for Enantiomers without Prior Resolution of Racemates, Angew. Chem., Int. Ed. Engl. **45** (6) (2006) 985-989. https://doi.org/10.1002/anie.200502302.
26. Le T. T. H., Tran L. H., Nguyen M. T., Pham M. Q., and Phung H. T. T. - Calculation of binding affinity of JAK1 inhibitors via accurately computational estimation, J. Biomol. Struct. Dyn. (2022) 1-11. https://doi.org/10.1080/07391102.2022.2118830.
27. Nguyen N. T., Nguyen T. H., Pham T. N. H., Huy N. T., Bay M. V., Pham M. Q., Nam P. C., Vu V. V., and Ngo S. T. - Autodock Vina Adopts More Accurate Binding Poses but Autodock4 Forms Better Binding Affinity, J. Chem. Inf. Model. **60** (1) (2019) 204-211. https://doi.org/10.1021/acs.jcim.9b00778.
28. Falé P. L. V., Araújo M. E. M., Ascensão L. and Serralheiro M. L. M. - Acetylcholinesterase inhibition by Rosmarinic acid from Plectranthus (Lamiaceae) species, Planta Med. **74** (09) (2008) 74-88. https://doi.org/10.1055/s-0028-1084086.
29. Liao Y., Hu X., Pan J. and Zhang G. - Inhibitory Mechanism of Baicalein on Acetylcholinesterase: Inhibitory Interaction, Conformational Change, and Computational Simulation, Foods **11** (2) (2022). https://doi.org/10.3390/foods11020168.
30. Liu X., Gao Z. G., Wu Y., Stevens R. C., Jacobson K. A., and Zhao S. - Salvianolic acids from antithrombotic Traditional Chinese Medicine Danshen are antagonists of human P2Y1 and P2Y12 receptors, Sci. Rep. **8** (1) (2018) 8084. https://doi.org/10.1038/s41598-018-26577-0.