

Original Research Article

Computer-aided drug discovery of the plausible action of curcuminoids and sesquiterpenes in regulating haemorrhage

Siwar Abu Saiefen¹, Beesan Arda², Donya Jarrar¹, Safwan Zbidat¹, Mira Khader¹, Siba Shanak^{1*}, Hilal Zaid^{3,4}

¹Faculty of Sciences, Arab American University, P.O Box 240, Jenin, ²Faculty of Sciences, Arab American University, Ramallah, ³Faculty of Medicine, Arab American University, P.O Box 240, Jenin, Palestine, ⁴Qasemi Research Center, Al-Qasemi Academic College, P.O Box 124, Baqa El-Gharbia 30100, Israel

*For correspondence: **Email:** siba.shanak@aaup.edu; **Tel:** 00970-4-2418888

Sent for review: 5 April 2025

Revised accepted: 18 February 2026

Abstract

Purpose: To elucidate the relationship between selected plant-derived phytochemicals and blood clotting mechanisms.

Methods: AutoDock 4.2 and Autodock tools 1.5.6 were used to find the best binding sites based on the scores of free energies and the equilibrium constants for binding. The best orientation for ligand-protein binding was studied, and the amino acids involved at the binding interface among selected phytochemicals of plant origin and each protein target were investigated.

Results: Demethoxycurcumin proved to be the most favorable *in silico* binding profile among the tested phytochemicals, as reflected by lower binding free energy values and inhibition constants across the four target proteins; however, experimental validation through *in vitro* and *in vivo* studies was required.

Conclusion: Demethoxycurcumin can plausibly aid in relieving blood coagulation. Further *in vitro*, *in vivo* and clinical studies can be conducted to verify this phytochemical as a potential drug.

Keywords: Haemorrhage, Factor XII, Factor XI, Factor IX, Factor VIII, Phytochemicals, *In silico*

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Hemostasis is a fundamental physiological mechanism that regulates blood circulation and protects the structural integrity of blood vessels. At the location of vessel damage, a highly organized network of more than 100 proteins activates a rapid and effective blood coagulation process [1]. This process is divided into intrinsic, extrinsic, and common pathways [2]. As a result of these pathways, prothrombin will be transformed into thrombin. Afterwards, soluble fibrinogen will be converted into insoluble fibrin

strands, which form the structural framework of blood clots [3]. This cascade of events is initiated when the activity of thrombogenic components increases or the activity of antithrombogenic components decreases [2].

The intrinsic pathway, also known as the contact activation pathway, is named so because it occurs entirely within the bloodstream with no external protein source required (e.g., a tissue factor) [4]. This pathway involves a series of proteolytic reactions that ultimately lead to the activation of factor ten (FX), a critical enzyme [5].

One of the key proteins in the intrinsic pathway is factor XII (FXII), also referred to as Hageman factor [6]. FXII initiates the cascade when it binds to negatively charged surfaces, such as exposed collagen in damaged blood vessels. As a result, it is also called contact activation pathway [7]. Upon activation, FXII will be transformed into FXIIa, which cleaves factor XI (FXI). FXI, in turn, activates factor IX (FIX) in the presence of calcium ions and other cofactors to become FIXa. FIXa, along with its cofactor, factor VIII (FVIII), forms a complex that activates FX, setting the stage for the common pathway of coagulation to proceed [8].

Understanding the intrinsic pathway and its associated proteins is of paramount importance in clinical medicine, and dysregulation of this pathway can lead to bleeding disorders, such as hemophilia. However, an overactive pathway can result in thrombotic events, e.g., deep vein thrombosis (DVT) and pulmonary embolism (PE). Several plant-derived phytochemicals have been reported to exhibit potential effects on platelet aggregation and coagulation pathways. Investigating their molecular interactions with key proteins of the intrinsic coagulation pathway may provide mechanistic insight into their possible therapeutic relevance.

This study aims to investigate the plausible interactions between five compounds: zingiberene, abscisic acid, curcumin, demethoxycurcumin, and humulone, alongside four proteins involved in the intrinsic pathway: fibrinogen, prothrombin, Hageman factor (Factor XII), and Factor XI (plasma thromboplastin antecedent).

METHODS

The PDB files were prepared for the docking protocol to study the five desired phytochemicals: curcumin, demethoxycurcumin, humulone, abscisic acid, and zingiberene. The process involved several critical steps. First, the SMILES (Simplified Molecular Input Line Entry System) representation for these compounds was acquired by systematically obtaining their IUPAC structures. This was facilitated using OPSIN, an open-source tool for chemical name-to-structure conversion [11]. An online SMILES translator and structure file generator were used to speed this procedure up, converting chemical structures into a format readable by the docking software. Open Babel facilitated this conversion seamlessly, ensuring the PDB files were correctly formatted and prepared for computational analysis [12].

To understand the potential interactions and binding affinities of the phytochemicals with their respective biological targets, these compounds were aligned with biological models using AutoDock, an advanced molecular docking software known for predicting the optimal binding orientation of small molecules to biological macromolecules [13]. Molecular docking simulations were performed using AutoDock 4.2 with AutoDockTools version 1.5.6. The binding energies and stability of the complexes formed between the phytochemicals and their target macromolecules were evaluated using an empirical scoring function in AutoDock. The best orientation was determined using a Lamarckian Genetic Algorithm (LGA). The Lamarckian Genetic Algorithm was applied with 100 runs, a population size of 150, a maximum number of energy evaluations of 2.5×10^6 , and a maximum number of generations of 27,000. Grid boxes were centered on the protein mass center and sized to fully encompass the binding interface of each protein. Water molecules were removed, while cofactors critical for protein function were retained. Polar hydrogen atoms were added, too [13].

The 3D structure files for the target proteins were used, including Coagulation factor XII (PDB ID: 4BDX) [14], Factor XIa (PDB ID: 7MBO) [15], fibrinogen (PDB ID: 1FZA) [16] and Prothrombin (PDB ID: 4UD9) [17]. These files included the examined holo-form PDB entries for the different target proteins when bound to positive control ligands crucial for protein function. The positive controls were removed from PDB entries for all proteins to achieve an apo- form.

The docking strategy involved thoroughly scanning the target protein's apo-form surface. The files were set up for docking with AutoDock 4.2, using the Lamarckian Genetic Algorithm for conformational searching [13]. AutoDockTools assigned ligand flexibility based on default settings for root atom selection and torsion assignment, adjusting the largest number of atoms while keeping the molecule's core relatively rigid.

The following x, y, and z dimensions were created for the grid boxes for the targeted proteins: (92 Å, 72 Å, 104 Å) for Coagulation factor XII; (126 Å, 126 Å, 126 Å) for Factor XIa; (67 Å, 126 Å, 80 Å) for fibrinogen, and (126 Å, 126 Å, 126 Å) for prothrombin. Grid dimensions were chosen to encompass the entire protein surface based on preliminary structural analysis. The mass's center was used as the origin. The resulting PDB files were extracted following the execution of the docking protocol. The PDB files

for the phytochemicals that displayed strong bonding with proteins were then examined after obtaining the best-scoring results. PyMol was used to examine, manipulate, and explore the 3D structures of molecules [18]. The resulting PDB files were analyzed to investigate the polar and non-polar interactions between each phytochemical and the protein.

RESULTS

The docking protocol was carried out for four proteins: fibrinogen, prothrombin, Hageman factor and Factor XIa, which are important factors involved in blood clotting, specifically in the intrinsic pathway. It is worth mentioning that the aim was to evaluate how these proteins interact with five selected phytochemicals (curcumin, demethoxycurcumin, abscisic acid, humulone and zingiberene).

Three main parameters were used to compare the results. The first was the binding free energy, which is a measure of the strength of interaction between the ligand and the target protein, where the lower values indicate stronger binding. The inhibition constant (K_i) is another parameter that represents the concentration at which 50% of the enzyme's activity is inhibited by the ligand, where the smaller K_i values indicate higher inhibitory potency. The third parameter is Root-Mean-Square Deviation (RMSD). It measures the structural deviation of the ligand from its initial docked conformation. Since most ligands lacked co-crystallized reference structures, RMSD primarily reflects deviation from the initial docked pose rather than a comparison to an experimental reference. Therefore, these values should be interpreted cautiously and not considered a validation of docking accuracy.

The RMSD was calculated relative to the input apo-form PDB structures. Since most ligands lacked co-crystallized reference poses, these RMSD values represent the deviation from the

initial docked conformation rather than a true experimental reference.

For the first protein, fibrinogen, the docking results (Table 1) show that curcumin stood out with the lowest binding free energy (-7.05 kcal/mol) and a relatively low K_i value, suggesting strong binding and inhibitory potential against fibrinogen; demethoxycurcumin also showed favorable characteristics with a low K_i value; zingiberene exhibited a high RMSD value; however, as no co-crystallized reference ligand was available, RMSD primarily reflects deviation from the initial docked conformation and should not be interpreted as a measure of docking reliability. These results suggested that curcumin, demethoxycurcumin, and zingiberene might be potential inhibitors of fibrinogen.

The presence of polar bonds between the protein and the phytochemical created a stronger binding interface compared to the nonpolar contacts, making it suitable for further *in vitro* tests. Figure 1 shows the interacting amino acids and the types of interactions.

Docking of prothrombin with five phytochemicals (Table 2) shows that abscisic acid had a positive binding free energy, indicating that it is not a favorable ligand for binding to prothrombin. The high positive energy suggests that it may not bind well to the target. Additionally, the absence of an inhibition constant (K_i) indicated that the compound might not be a strong inhibitor of prothrombin. Among the tested phytochemicals, demethoxycurcumin and zingiberene showed the strongest binding affinities and inhibitory potential for prothrombin, while abscisic acid had the least favorable binding characteristics.

As Table 2 shows, there were no polar interactions between prothrombin and the last two phytochemicals, suggesting that the binding will be weak. Figure 2 shows the interacting amino acids and the types of interactions.

Table 1: Binding free energies, inhibition constants, structure deviation from the reference structure, number of polar contacts and names of amino acids involved in polar interactions for docking the phytochemicals to fibrinogen (protein)

Ligand	AutoDock binding free energy (kcal/mol)	Inhibition constant, K_i (nM)	RMSD from reference structure (Å)	No. of polar contacts	Amino acids involved in polar interactions
Curcumin	-7.05	6810	34.801	5	(3) TYR and (2) THR
Demethoxycurcumin	-7.07	6560	34.082	7	TRP, GLY, TYR, (2) THR, VAL and TYR
Abscisic acid	-6.34	22390	31.805	3	SER, THR and GLY
Humulone	-6.54	16000	32.473	4	TYR, (2) GLY and THR
Zingiberene	-7	7440	29.33	0	None

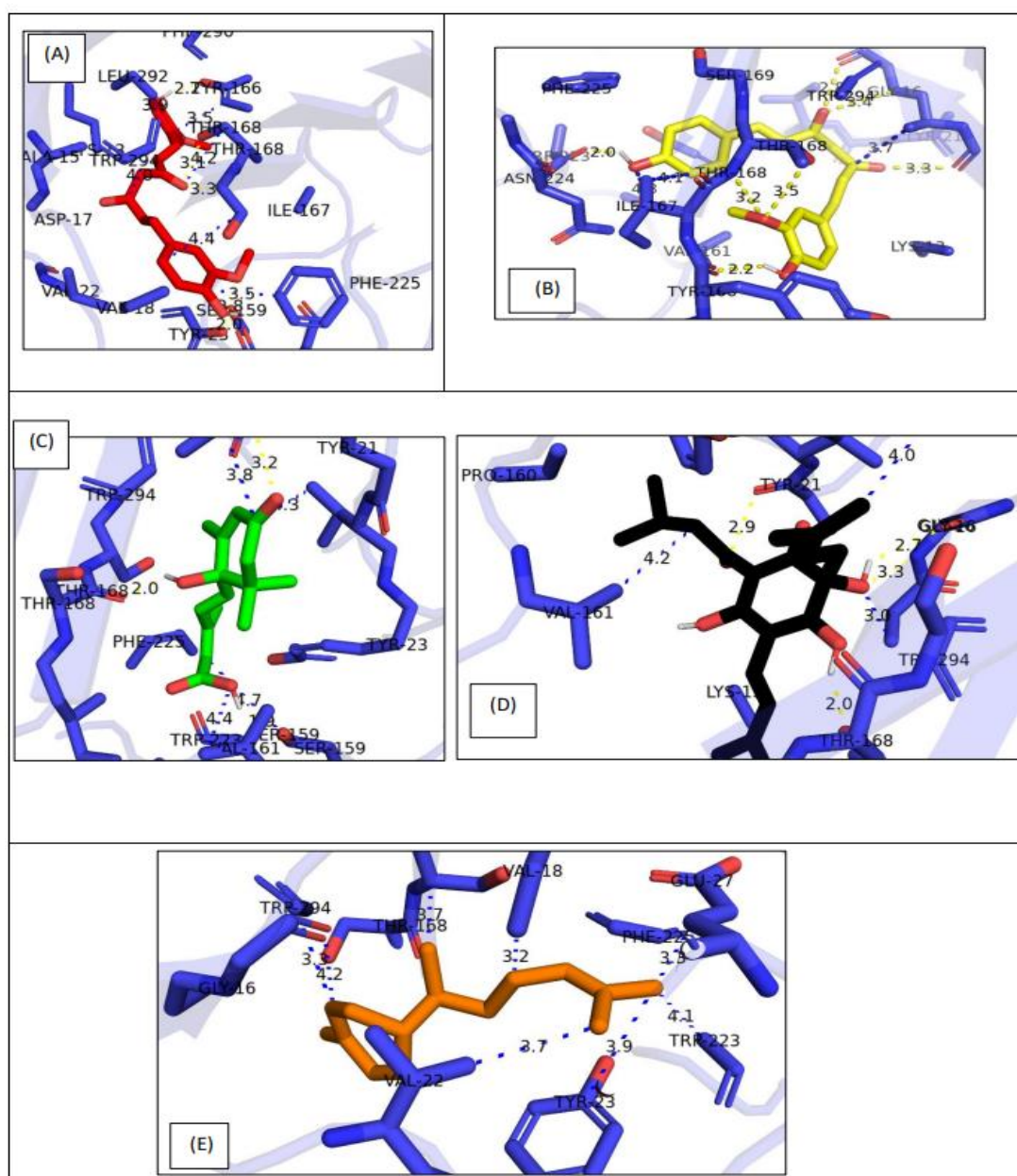


Figure 1: (A) Fibrinogen with curcumin, (B) Fibrinogen with demethoxycurcumin, (C) Fibrinogen with abscisic Acid (D) Fibrinogen with humulone and (E) Fibrinogen with zingiberene. Blue bonds represent nonpolar interactions, and yellow bonds represent polar interactions

Table 2: Binding free energies, inhibition constants, structure deviation from the reference structure, number of polar contacts, and names of amino acids involved in polar interactions for docking the phytochemicals to prothrombin (protein)

Ligand	AutoDock binding free energy (kcal/mol)	Inhibition constant, Ki (nM)	RMSD from reference structure (Å)	No. of polar contacts	Amino acids involved in polar interactions
Curcumin	-7.66	2410	27.958	2	Asp, HIS.
Demethoxycurcumin	-10.83	11.54	26.119	6	SER, ARG, ASP, Glu, TYR, SER
Abscisic acid	51.79		22.743	2	THR, ASP.
Humulone	-7.47	3360	28.33	0	None
Zingiberene	-7.93	1540	25.867	0	None

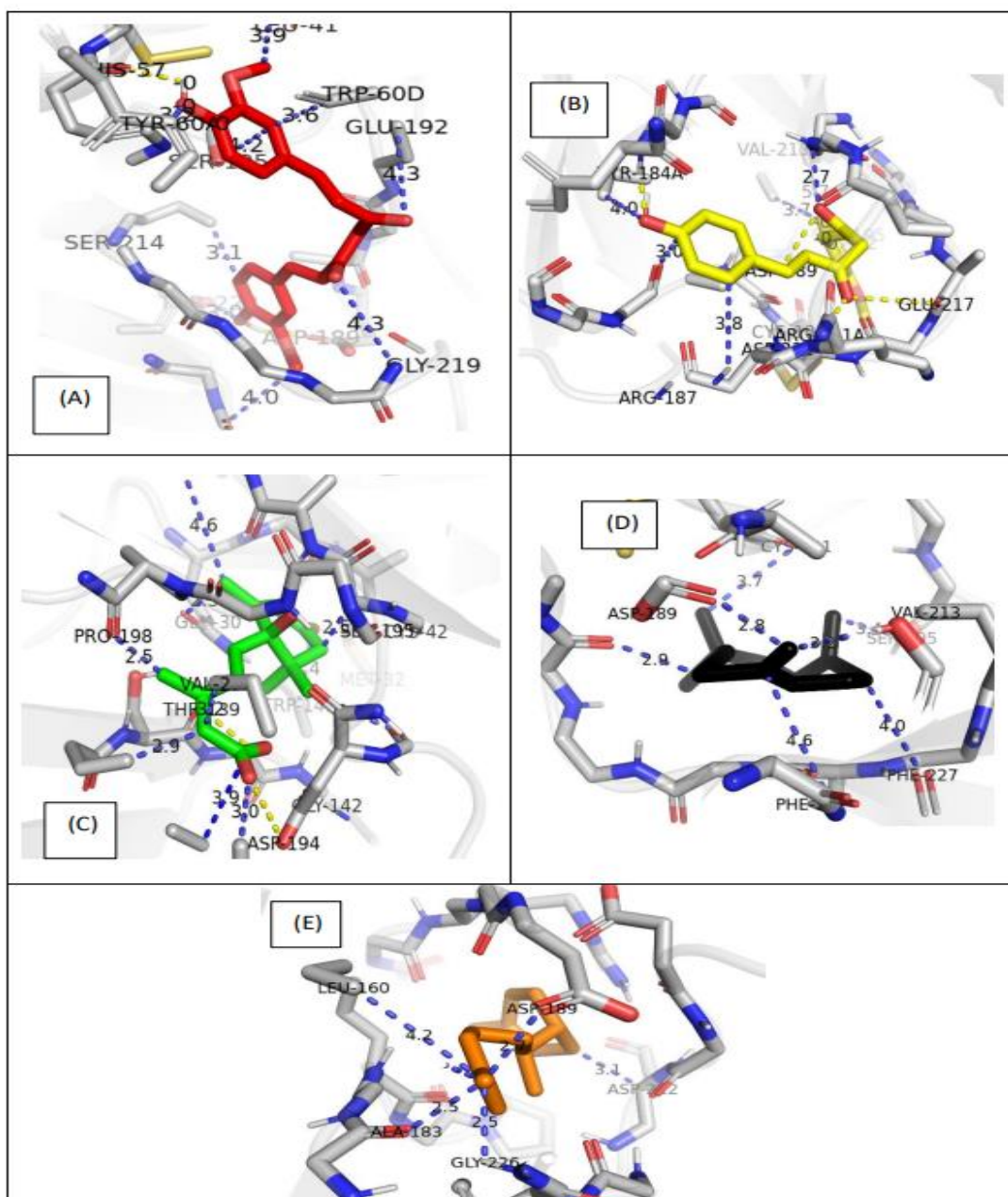


Figure 2: (A) Prothrombin with curcumin, (B) Prothrombin with demethoxycurcumin, (C) Prothrombin with abscisic Acid (D) Prothrombin with humulone and (E) Prothrombin with zingiberene. Blue bonds represent non-polar interactions, and yellow bonds represent polar interactions

Hageman factors docking results (Table 3) indicated that curcumin and demethoxycurcumin had the most favorable binding characteristics with Hageman factor among the tested ligands. They exhibited the lowest binding free energies, inhibition constants, and a reasonable number of polar contacts. However, the relatively high RMSD values suggested that these ligands might not perfectly fit the protein's binding site. Further studies, including experimental validation, might be needed to confirm their binding affinity and

efficacy as potential inhibitors or modulators of Hageman factor. Figure 3 shows the interacting amino acids of Hageman factor and the types of interactions with the different docked ligands.

The docking results for the last protein, Factor XIa (Table 4), show that curcumin appeared to be the most promising ligand among the five, with the lowest binding free energy (-8.46 kcal/mol) and the lowest K_i value (631.16 nM), indicating strong binding and inhibitory potential.

Demethoxycurcumin also shows favorable characteristics with a relatively low RMSD value (20.782 Å). These results suggested that curcumin and demethoxycurcumin might be

worth further investigation for their potential as inhibitors of Factor XIa. Figure 4 shows the interacting amino acids in Factor XIa and the types of interactions.

Table 3: Binding free energies, inhibition constants, structure deviation from the reference structure, number of polar contacts and names of amino acids involved in polar interactions for docking the phytochemicals to Hageman factor (protein)

Ligand	AutoDock binding free energy (kcal/mol)	Inhibition constant, Ki (nM)	RMSD from reference structure (Å)	No. of polar contacts	Amino acids involved in polar interactions
Curcumin	-8.27	859.89	22.025	5	GLN, ILE, TYR, CYS, ARG
Demethoxycurcumin	-8.51	581.64	22.943	2	TYR, ILE
Absciscic acid	-6.63	13740	20.228	4	GLY (2), CYS and ARG
Humulone	-7.71	2220	22.487	4	CYS (2), TYR (2)
Zingiberene	-7.06	6650	20.961	0	None

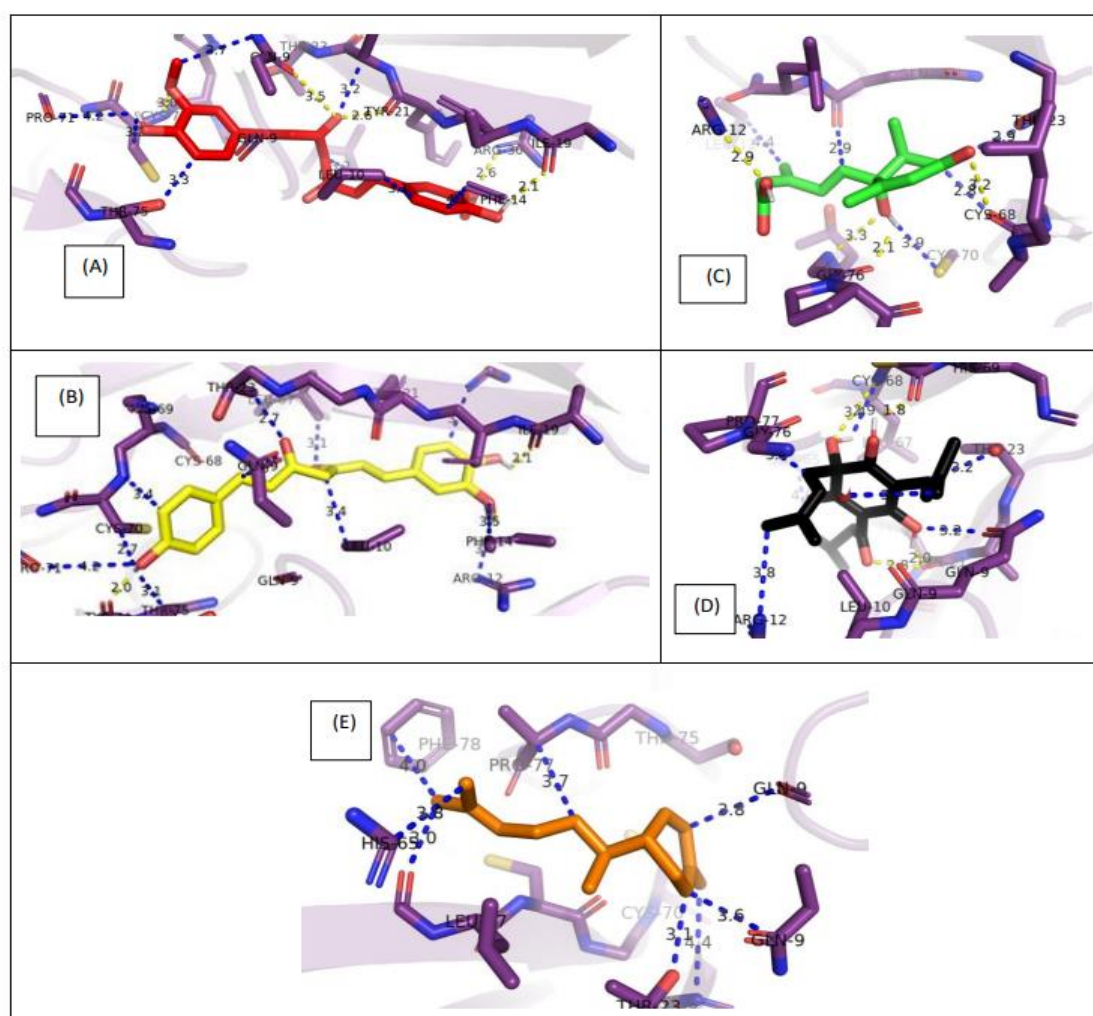


Figure 3: (A) Hageman factor with curcumin, (B) Hageman factor with demethoxycurcumin, (C) Hageman factor with absciscic Acid (D) Hageman factor with humulone and (E) Hageman factor with zingiberene. Blue bonds represent non-polar interactions, and yellow bonds represent polar interactions

Table 4: Binding free energies, inhibition constants, structure deviation from the reference structure, number of polar contacts, and name of amino acids involved in polar interactions for docking the phytochemicals to Factor Xla antecedent (protein)

Ligand	AutoDock binding free energy (kcal/mol)	Inhibition constant, Ki (nM)	RMSD from reference structure (Å)	No. of polar contacts	Amino acids involved in polar interactions
Curcumin	-8.46	631.16	21.621	8	VAL, ASP, CYS, SER (2), ASP and GLY
Demethoxycurcumin	-7.77	2020	20.782	7	ASP, CYS, SER (2), GLY, ASP and CYS
Absciscic acid	-7.81	1900	22.764	6	GLY (2), SER (2), GLY and ASP
Humulone	-6.43	19490	23.491	6	GLU (2), SER, GLY and GLY (2)
Zingiberene	-6.23	27050	23.582	0	None

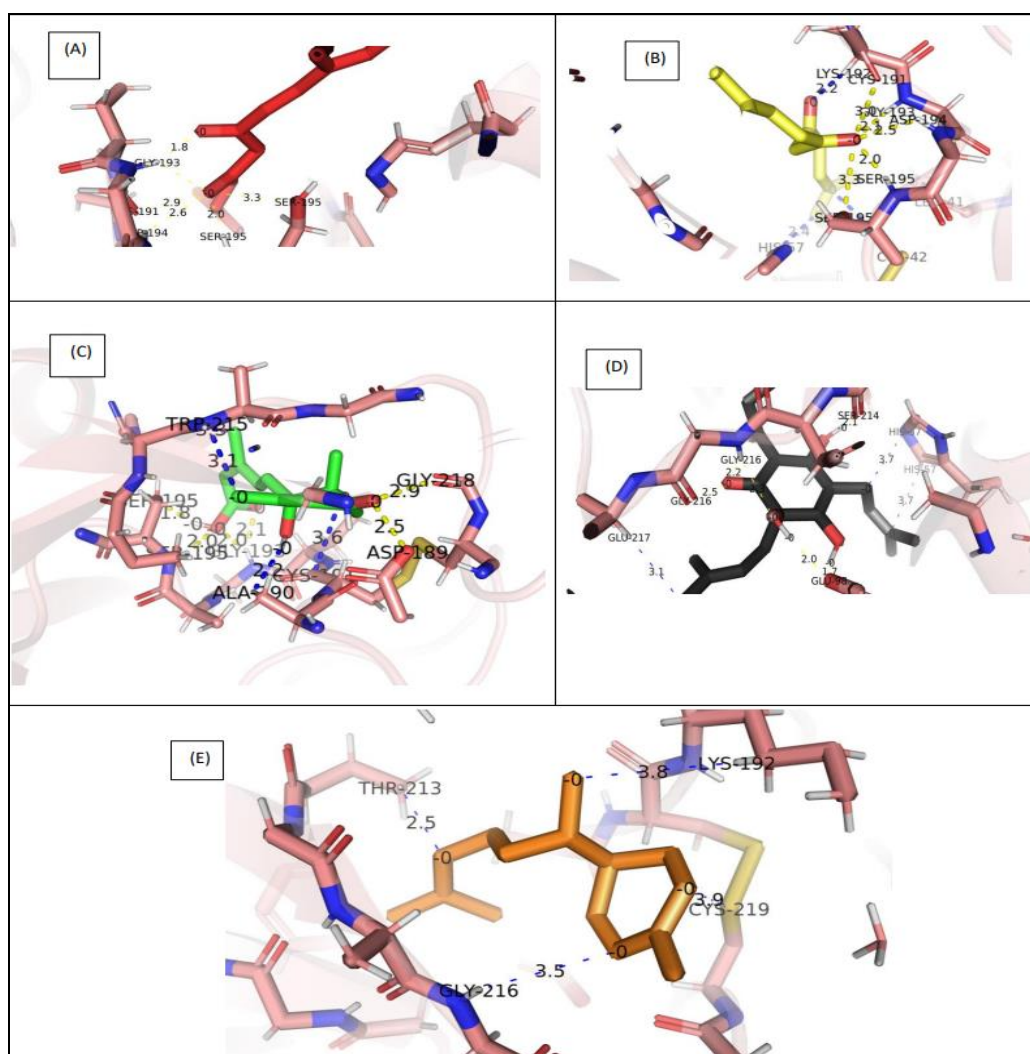


Figure 4: (A) Factor Xla antecedent with curcumin, (B) Factor Xla with demethoxycurcumin, (C) Factor Xla with absciscic Acid (D) Factor Xla with humulone and (E) Factor Xla with zingiberene. Blue bonds represent non-polar interactions, and yellow bonds represent polar interactions

To validate the docking protocol, a re-docking approach was performed using milvexian, the co-crystallized and experimentally validated inhibitor of Factor Xla antecedent (PTA; activated

coagulation factor Xla, FXla). Milvexian was extracted from the crystal structure of the FXla–milvexian complex (PDB ID: 7MBO) and re-docked into the same binding site, after which

the docked poses were compared with the crystallographic binding mode using root-mean-square deviation (RMSD) analysis of ligand heavy atoms following optimal superposition. Among the 50 poses generated by AutoDock4, validation was focused on the 10 poses exhibiting the lowest RMSD values, as these represent the most reliable reproductions of the experimental binding mode. For these top-ranked poses, RMSD values showed a narrow distribution with an average of 2.29 ± 0.03 Å, indicating a high degree of structural consistency. In addition, the lowest-energy pose ($\Delta G = -7.33$ kcal/mol) displayed an RMSD of 2.27 Å relative to the crystallographic ligand, further supporting the ability of the docking protocol to reproduce the experimentally observed binding orientation of milvexian within the active site of Factor Xla antecedent. Notably, none of the other protein structures included in this study contained a co-crystallized inhibitor; therefore, re-docking-based validation was feasible only for milvexian. To validate the docking protocol, the predicted binding poses of milvexian were quantitatively compared with the experimental reference conformation in complex with human coagulation factor Xla (PDB ID: 7MBO) using root-mean-square deviation (RMSD) analysis. RMSD values were calculated for ligand heavy atoms after optimal superposition relative to the reference milvexian structure extracted from the 7MBO complex. Across the 50 docked poses generated by AutoDock4, RMSD values ranged from 2.24 to 3.97 Å, with an average RMSD of 3.17 ± 0.67 Å (mean $\pm$ standard deviation). Importantly, the lowest-energy docked pose ($\Delta G = -7.33$ kcal/mol) exhibited an RMSD of 2.27 Å compared with the experimental binding mode, indicating a close agreement between the predicted and crystallographic ligand orientations. Collectively, these results demonstrate that the docking protocol reliably reproduces the experimentally observed binding mode of milvexian within the active site of factor Xla, supporting the robustness and validity of the docking methodology employed in this study.

DISCUSSION

Selected plant-derived phytochemicals were investigated and their possible binding to biological targets (fibrinogen, prothrombin, Factor Xla and Hageman factor) was examined, too. The strong binding might consequently indicate a possible activation of intrinsic and extrinsic pathways of blood coagulation. It should be noted that the present study employed rigid docking, which does not account for protein flexibility and may overestimate binding affinities.

Future studies incorporating molecular dynamics simulations and experimental assays are necessary to validate the stability and biological relevance of the predicted interactions. Additionally, enzyme assays need to be carried out to confirm whether the binding processes are inhibitory or activatory.

The study was conducted to provide exploratory results about the phytochemical compounds that could be used in studies for the activation of coagulation processes. The results indicated that there was a strong yet differential binding between several tested phytochemicals and the targeted proteins. The current work was nonetheless conducted using rigid docking, which gives a rough estimation for the binding free energies when compared to flexible docking. However, the analysis introduced prior knowledge about the tested compounds *in silico* and served as a basis for future *in vitro* studies.

Curcumin, demethoxycurcumin, abscisic acid, zingiberene, and humulone showed favorable docking results on the active site of fibrinogen, making them plausible candidates for further experiments. In the docking results, the compounds bind to the whole protein surface with strong bonds. The existence of polar bonds makes the binding stronger and the test for binding more accurate and useful. Only zingiberene showed no polar bonds, although it showed good docking results.

For prothrombin protein, docking results showed that four out of the five phytochemicals interacted strongly with the protein, scanning the whole protein surface (curcumin, demethoxycurcumin, zingiberene and humulone), while abscisic acid showed a positive AutoDock binding free energy (+51.79 kcal/mol), which indicated that there was no real binding even though it had two polar bonds. Both curcumin and demethoxycurcumin phytochemicals introduced binding with more than one polar bond, making them feasible lead compounds for further studies. The binding free energies for the majority of phytochemicals to the prothrombin showed very low inhibition constants, in the low range of micromolars, and demethoxycurcumin in the nanomolar range (except abscisic acid, which had no inhibition constant), introducing prothrombin as a hub target in a possible activation of intrinsic and extrinsic pathways of blood coagulation.

For Hageman factor, good ranges of AutoDock binding free energies (-8.51 to -6.63 kcal/mol) and inhibition constants (581.64 nM to 13,740 nM) for scanning the whole protein surface were found for five phytochemicals (curcumin, demethoxycurcumin, humulone, zingiberene and

abscisic acid). However, scanning the binding interface introduced polar binding for all phytochemicals except zingiberene.

For Factor XIa, good ranges of AutoDock binding free energies (-8.46 to -6.23 kcal/mol) and inhibition constants (631.16 to 27,050 nM) were found, and all phytochemicals showed at least four polar bonds except for zingiberene, which had no polar bonds with Factor XIa.

In all four proteins, zingiberene showed no polar bonds, whereas curcumin, demethoxycurcumin and abscisic acid consistently formed at least one polar bond with all four proteins. However, available studies on ginger and bleeding are not conclusive. While some studies indicated a potential link between ginger and increased bleeding risk, others report conflicting results, suggesting that ginger might not significantly impact bleeding in most individuals [10]. Moreover, the doses and forms of ginger used in these studies vary.

From a tropical medicine perspective, the findings of this study are particularly relevant due to the widespread availability, low cost, and traditional use of ginger in tropical and subtropical regions. In settings where access to conventional pharmacological agents for managing bleeding or coagulation disorders is limited, plant-derived compounds may offer complementary or supportive therapeutic options. Although the present findings are based on *in silico* analysis and do not account for protein flexibility or biological complexity, they provide a mechanistic framework that may guide future experimental and clinical investigations focused on developing affordable and accessible interventions for coagulation-related disorders in tropical regions.

CONCLUSION

Certain plant-derived phytochemicals may exhibit modulatory effects on coagulation-related targets, which means it would disturb the blood clotting process. A group of phytochemicals derived from ginger that may be responsible for the clotting process includes curcumin, demethoxycurcumin, humulone, abscisic acid, and zingiberene. In terms of binding affinity constants and free energies, curcumin, demethoxycurcumin, and zingiberene demonstrated outstanding outcomes when targeting a number of proteins, including fibrinogen, coagulation factor XII, factor XIa, and prothrombin, which are important factors in the intrinsic pathway. Particular attention should be paid to demethoxycurcumin, which displayed the

best docking outcomes. Demethoxycurcumin also made an important distinction in polar bonds with proteins.

DECLARATIONS

Acknowledgement/Funding

We would like to thank the Arab American University- Palestine for its financial support. This work was supported by the Arab American University (AAUP) research foundation.

Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Use of research reporting tools

We confirm that this molecular docking study has been prepared in accordance with WAME recommendations and follows principles of transparent and reproducible research reporting, with all computational methods clearly described.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Conceptualization, S. Shanak; Data curation, S. Abu Saiefen, D. Jarrar, S. Zbidat, and S. Shanak; Formal analysis, S. Abu Saiefen, B. Arda, D. Jarrar, S. Zbidat, and S. Shanak; Funding acquisition, H. Zaid, and S. Shanak; Investigation, H. Zaid, and S. Shanak; Methodology, S. Abu Saiefen, B. Arda, D. Jarrar, S. Zbidat, S. Shanak, and H. Zaid; Supervision, H. Zaid and S. Shanak; Validation, S. Shanak;

Original draft writing, S. Abu Saiefen, D. Jarrar, S. Zbidat, M. Khader, and S. Shanak; Formal analysis, S. Abu Saiefen, B. Arda, D. Jarrar, S. Zbidat, M. Khader, and S. Shanak. All authors have read and agreed to the published version of the manuscript.

REFERENCES

- Oldenburg J, Schwab R. Molecular biology of blood coagulation. *Semin Thromb Hemost* 2001; 27(4): 313-324. doi: 10.1055/s-2001-16885.
- Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian J Anaesth* 2014; 58(5): 515-523. doi: 10.4103/0019-5049.144643.
- Chinnaraj M, Planer W, Pozzi N. Structure of coagulation Factor II: Molecular mechanism of thrombin generation and development of next-generation anticoagulants. *Front Med (Lausanne)* 2018; 5: 281. doi: 10.3389/fmed.2018.00281.
- Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. *Crit Rev Biochem Mol Biol* 2015; 50(4): 326-336. doi: 10.3109/10409238.2015.1050550.
- Kattula S, Byrnes JR, Wolberg AS. Fibrinogen and Fibrin in hemostasis and thrombosis. *Arterioscler Thromb Vasc Biol* 2017; 37(3): e13-e21. doi: 10.1161/atvbaha.117.308564.
- Caen J, Wu Q. Hageman factor, platelets and polyphosphates: early history and recent connection. *J Thromb Haemost* 2010; 8(8): 1670-1674. doi: 10.1111/j.1538-7836.2010.03893.x.
- Maas C, Renné T. Coagulation factor XII in thrombosis and inflammation. *Blood* 2018; 131(17): 1903-1909. doi: 10.1182/blood-2017-04-569111.
- Wheeler AP, Gailani D. The intrinsic pathway of coagulation as a target for antithrombotic therapy. *Hematol Oncol Clin North Am* 2016; 30(5): 1099-1114. doi: 10.1016/j.hoc.2016.05.007.
- Coban A, Bornberg-Bauer E, Kemena C. Domain evolution of vertebrate blood coagulation cascade proteins. *J Mol Evol* 2022; 90(6): 418-428. doi: 10.1007/s00239-022-10071-3.
- Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO. Effect of ginger on platelet aggregation and eicosanoid synthesis in humans. *Prostaglandins Leukot Essent Fatty Acids* 2005; 72(5): 387-391.
- Lowe DM, Corbett PT, Murray-Rust P, Glen RC. Chemical name to structure: OPSIN, an open source solution. *J Chem Inform Modeling* 2011; 51(3): 739-753. doi: 10.1021/ci100384d.
- O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. *J Cheminformatics* 2011; 3: Art no. 33, doi: 10.1186/1758-2946-3-33.
- Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility. *J Computational Chemistry* 2009; 30(16): 2785-2791, 2009, doi: 10.1002/jcc.21256.
- Beringer D, Kroon-Batenburg L. The structure of the Fnl-EGF-like tandem domain of coagulation factor XII was solved using SIRAS. *ACTA Crystallographica Section F-Struct Biol Communicat* 2013; 69: 94-102, 2013, doi: 10.1107/S1744309113000286.
- Dilger AK, Pabbisetty KB, Corte JR, De Lucca I, Fang T, Yang W, Pinto DJP, Wang Y, Zhu Y, Mathur A, et al. Discovery of milvexian, a high-affinity, orally bioavailable inhibitor of Factor XIa in clinical studies for antithrombotic therapy. *J Med Chem* 2022; 65(3): 1770-1785. doi: 10.1021/acs.jmedchem.1c00613.
- Spraggon G, Everse SJ, Doolittle RF. Crystal structures of fragment D from human fibrinogen and its crosslinked counterpart from fibrin. *Nature* 1997; 389(6650):455-62. doi: 10.1038/38947.
- Ruehmann E, Betz M, Heine A, Klebe G. Fragment binding can be either more enthalpy-driven or entropy-driven: crystal structures and residual hydration patterns suggest why. *J Medical Chem* 2015; 58: 6960-6971. doi: 10.1021/acs.jmedchem.5b00812.
- Yuan S, Chan H, Hu Z. Using PyMOL as a platform for computational drug design. *Wiley Interdiscipl Rev-Comput Molecular Sci*. Ed 2017; 7.