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Membrane-stabilizing and clot-lysing capacity of *Coriandrum sativum* ethanolic extract and one of its major components called linalool

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Abstract

Background *Coriandrum sativum* L. is well known for its usage in traditional medicine and cooking. This herb is commonly known as coriander as well as cilantro. *C. sativum* possesses many important phytochemical groups, including polyphenols, vitamins, and phytosterols, with promising biological activities such as antioxidant, anti-inflammatory, anticancer, anti-antidiabetic, neuropharmacological, and so on. This study aimed to assess the membrane-stabilizing and clot-lysis capacity of *C. sativum* ethanol extract (ECS) and its major component, linalool (LIN).

Methods In-vitro membrane-stabilizing action of ECS and LIN was performed by using hemolysis of human red blood cells (HRBCs) and egg albumin protein denaturation techniques, and clot lysis activity was observed by human clotted blood techniques. Further, we observed in-silico studies.

Results ECS and LIN showed significant ($p < 0.05$) membrane-stabilizing and clot-lysing capacity compared to the control group in a concentration-dependent manner. The highest inhibition of hemolysis by the ECS was observed at 160 µg/mL by 77.61 ± 0.01%, while LIN demonstrated 52.32 ± 0.01%. Further, in the egg-albumin protein denaturation test, ECS and LIN demonstrated 27.62 ± 0.01% and 46.74 ± 0.02% membrane protection, respectively. At 160 µg/mL, ECS and LIN showed clot lysis activity of 18.02 ± 3.968% and 52.32 ± 0.01%, respectively. In our in-silico studies, LIN exhibited significant binding interactions with different inflammatory mediators and clot lysis factors.

Conclusion ECS showed strong membrane-stabilizing and moderately clot-lysing activity in our studies, and it may be possible due to the presence of the major component LIN.

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Keywords *Coriandrum sativum*, Inflammation, Atherothrombosis

Introduction

Plants, minerals, and animal products have historically been the main sources of medicines, and the utilization of natural materials with therapeutic properties dates back to the dawn of human civilization [1]. Throughout the last few decades, natural products have played a supporting role in medication discovery and development [2]. Studies have been conducted all around the world to confirm their efficacy, and some of the results have prompted the development of plant-based medications [3].

Coriander is a highly popular medicinal plant due to its massive medicinal value [4]. All parts of this plant are used as remedies for the treatment of different disorders in traditional medicinal systems from ancient civilizations [5]. The herbaceous plant coriander is a plant from the family *Apiaceae* (*Umbelliferae*) [6]. The main source of the essential oils is dried fruits. It is extensively cultivated in Southeast Asian countries, central Europe, and Mediterranean countries [7]. India, Pakistan, Iran, Turkey, the Soviet Union, Hungary, Poland, Romania, the Czech Republic, Slovakia, Morocco, Canada, Guatemala, Mexico, and Argentina are the top coriander-producing countries. The herbal plant *C. sativum* contains essential oils, which are found in the leaves, flowers, and mainly fruits of the plant [8]. Apart from the essential oils, other phytochemicals are also found in this herb. Linalool (LIN), α-pinene, terpineol, citronellol, geraniol, and geranyl acetate are the phytochemicals that are present in *C. sativum* [9]. LIN is the major constituent of *C. sativum*, and the concentration range of LIN in *C. sativum's* oil is about 57.5–75.1% [10]. Previous studies suggest that *C. saivum* possesses diverse biological activities, including antioxidant, anti-inflammatory, and anti-microbial activity [11]. LIN is also evident to exert many pharmacological effects, including antioxidant, anti-inflammatory, and organ-protective capacity [12].

Membrane destabilization is a complex process driven by the interaction of external agents, such as proteins and toxins, with the lipid bilayer enveloping cells [13]. This interaction disrupts the delicate balance of the membrane, altering its fluidity and permeability [14]. Environmental factors, like changes in temperature and pH, can further exacerbate this destabilization [15]. The consequences are significant, influencing critical cellular functions such as signaling and apoptosis [16]. Understanding the mechanisms behind membrane destabilization is essential for uncovering fundamental aspects of cell biology and exploring potential therapeutic interventions for diseases associated with compromised membrane integrity [17]. Carbamazepine, Gabapentin, Mexilitine, Oxcarbazepine, Phenytoin, Valproic Acid, Topiramate, and Zonisamide are commonly used membrane stabilizers [18]. However, these medications come with potential side effects like sedation, dizziness, hematologic changes, nausea, the formation of kidney stones, renal calculi, and others [19].

Atherothrombosis is the formation of a blood clot (thrombus) within a blood vessel that has been narrowed by the buildup of fatty deposits (atherosclerosis) [20]. Atherosclerosis is a chronic condition in which fatty substances, cholesterol, cellular waste products, calcium, and other materials accumulate within the walls of arteries, forming plaques [21]. These plaques can gradually narrow and stiffen the arteries, limiting blood flow to vital organs and tissues [22]. When the surface of an atherosclerotic plaque becomes disrupted or damaged, the body's natural clotting mechanisms can be triggered, leading to the formation of a blood clot or thrombus [23]. This clot can further narrow the already compromised blood vessel, potentially leading to partial or complete blockage [24]. If this occurs in a coronary artery (supplying the heart), it can result in a heart attack (myocardial infarction) [25]. If it occurs in a cerebral artery (supplying the brain), it can lead to a stroke [26]. Atherothrombosis is a significant contributor to cardiovascular diseases, which are the leading cause of death worldwide [27]. Clot-lysing drugs, also known as thrombolytics, are essential in treating conditions like heart attacks and strokes by dissolving blood clots [28]. Alteplase, Reteplase, Tenecteplase, Urokinase, Prourokinase, and Anistreplase (APSAC): these medications are used as thrombolytics or clot-lysing drugs [29]. However, their use comes with potential side effects, most notably an increased risk of bleeding [30]. This risk necessitates careful consideration, particularly in patients with a history of bleeding disorders or recent surgeries [31].

This study aimed to evaluate the membrane-stabilizing and clot-lysis capacity of *C. sativum* ethanolic extract and one of its major components, LIN, using some in-vitro test models and in-silico studies.

Materials and methods

In-vitro studies

Collection and extraction of test sample

Fresh-dried seeds of *C. sativum* were purchased from a local market in Dhaka at the end of the winter season. The sample was identified by Prof. Dr. Shaikh Bokhtear Uddin, Chittagong University, Chattogram, Bangladesh (identified specimen number: SG-21012024-006). The seeds were isolated from adulterants (e.g., sand particles, seeds of other herbs, etc.) and ground into coarse

powder. The powdered materials were preserved in an amber-colored bottle until the extraction commenced. Approximately 500 g of coarse seed powder was soaked in 1200 mL of absolute ethanol in an amber-colored glass jar (capacity: 2.5 L) for 14 days. The content was gently shaken occasionally. On the 15th day the soaked materials were filtered through Whatman filter paper number 1, and the extract was collected after drying the filtrate at room temperature. The percentage of yield value of ECS was calculated using the following formula:

$$\text{Yield}\,(\%) = [\text{Extract weight} \div \text{Powder weight}] \times 100$$

Chemicals and reagents

Ethanol, tween 80, and other chemicals and reagents were bought from Merck (India). Streptokinase (Durakinase) was purchased from Dongkook Pharmaceutical Co. Ltd. (South Korea), while acetylsalicylic acid (ASA) and propranolol (PPL) were kindly provided by ACME Laboratories Ltd. and ACI Ltd., Bangladesh, respectively.

Ethical concerns

This study was approved and funded by the Bangabandhu Sheikh Mujibur Rahman Science and Technology University Research Center (BSMRSTU-RC) (Approval No. 2023-33).

Membrane stabilization studies

HRBC test This study was conducted using the model developed by Shinde et al. [32] with some modifications. Initially, 5 ml of fresh blood was collected from a healthy donor (human) and mixed with dipotassium salt of EDTA (2.2 mg/mL). The blood cells were then accumulated by centrifugation at 3000 × *g* for 10 min and washed thrice with an isotonic solution (154 mM NaCl) in 10 mM sodium phosphate buffer (pH 7.4). The resulting cell suspension was re-centrifuged at 3000 × *g* for 10 min and finally re-suspended in an equal volume of isotonic buffer solution. Next, 0.5 mL of the cell suspension was added to a mixture of 5 mL of hypotonic solution (50 mM NaCl) and 0.5 mL of the test (ECS, LIN) or standard (PPL) solution (10, 20, 40, 80, and 160 µg/mL) in 10 mM sodium phosphate-buffered saline (pH 7.4), as specified. The control tube contained only 0.5 ml of cell suspension and 5 mL of hypotonic solution in the above-mentioned buffer. The reaction mixture was incubated for 10 min at room temperature and centrifuged at 3000 × *g* for 10 min. Finally, the optical density (OD) of the supernatant was quantified at 540 nm using a colorimeter (AE-11 M, Japan). The percentage inhibition of hemolysis was calculated using the following equation:

$$\%\text{Inhibition of hemolysis} = \{(\text{OD}_{\text{control}}\text{OD}_{\text{testsamples}})/\text{OD}_{\text{control}}\} \times 100$$

The half-minimal inhibitory concentration (IC_{50}) was measured utilizing non-linear regression analysis with the aid of Graph Pad Prism software (version: 6.5).

Egg-albumin test This study was done according to the method described by Dharmadeva et al. [33] with slight modifications. Briefly, test samples (ECS, LIN) and standard drug (ASA) concentrations were prepared as per the HRBC method. Reaction mixtures were prepared using 2.8 mL of phosphate-buffered saline (pH 6.4) and 0.2 mL of egg albumin (from fresh hen's egg). Then 2 mL of test/control from each different concentration were mixed gently with reaction mixtures. Distilled water was used as a negative control. Then the reaction mixtures were incubated in a water bath at 37 ± 2 °C for 15–20 min, and later, they were heated at 70 °C, at which point the reaction mixture was maintained for 5 min. Then, the reaction mixture was allowed to cool down at room temperature for 15 min. Absorbance of the reaction mixture before and after denaturation was measured for each concentration at 680 nm using a colorimeter (AE-11 M, Japan). Each test was repeated thrice, and the mean absorbance was recorded. The percentage of inhibition of egg protein was determined on a percentage basis with respect to control using the following formula.

$$\text{Percentage inhibition}\,(\%) = \left[\left(\begin{matrix}\text{Absorbance of control} - \\ \text{Absorbance of test}\end{matrix}\right) \div \text{Absorbance of control}\right] \times 100$$

Clot lysis test

This in-vitro study was done according to the model developed by Prasad et al. [34]. In this case, we collected blood samples from 3 healthy donors having no record of oral contraceptives or anticoagulant drugs history for the last three months. Then we distributed 0.5 mL of fresh blood in pre-weighed microcentrifuge tubes. After incubating the blood sample at 37 °C for 45 min, the serum was cautiously excluded without disturbing the clot, and tubes were weighed. 100 µL of test sample at different concentrations (10, 20, 40, 80, and 160 µg/mL) was added in each tube. 100 µL of streptokinase (equiv. 30,000 IU) and 100 µL of DW were added to the positive control and control-marked tubes, respectively. After incubation of the tubes at 37 °C for 90 min, the discharged fluid from each tube was carefully removed, and the tubes were

reweighed. The percentage of clot lysis was calculated as follows:

$$\%\text{Clot lysis} = (\text{Weight of clot after treatment} \div \text{Weight of clot before treatment}) \times 100$$

The half-minimum inhibitory concentration (IC_{50}) value for the test sample was also determined as mentioned above.

Statistical analysis

Values are expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was followed by the Newman Keuls *post host* test using the GraphPad Prism software (version 6.5), considering $p < 0.05$ at 95% confidence intervals.

Molecular docking (in-silico) study

Preparation of macromolecule

The protein sequence of inflammatory mediators Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), Nuclear Factor Kappa B Subunit 1 (NFKB1), and Nuclear Factor Kappa B Subunit 2 (NFKB2), Transient Receptor Potential Cation Channel Subfamily A Member 1 (TRPA1), Transient Receptor Potential Cation Channel Subfamily V Member 1 (TRPV1), Tissue Plasminogen Activator (tPA), and Urokinase Plasminogen Activator (uPA) were obtained from the RCSB Protein Data Bank (PDB) (PDB ID: 5Z62 (A chain), 5Z62 (B chain), 1nfi, 1a3q, 6hc8, 8gf8, 1a5h, and 1c5y), respectively. Macromolecules were prepared using PyMOL v1.7.4.5 Edu software, and energy minimization of protein molecules was achieved by using the Swiss-PDB Viewer software package (version 4.1.0) before docking.

Ligand preparation

The chemical structure of LIN (PubChem ID: 6569) was obtained from the PubChem repository sample in the 3D 'sdf' file format. With the Chem3D Pro21.0 software (PerkinElmer Informatics, Inc., Boston, MA, USA) packages, all of the ligands' internal energies were optimized.

Docking protocol

The significance of molecular docking for the creation of novel medications has increased. Through the use of the PyRx virtual screening tool, molecular docking is a sort of computer modeling that facilitates the prediction of the preferred binding orientation of one molecule (a ligand, for example) to another (a receptor, for example) when they interact to form a stable complex. After preparing the ligands and macromolecules (proteins), we performed molecular docking with ligands and proteins using the PyRx-0.8 virtual assessment tool (version 0.8.0.0, The Scripps Research Institute, La Jolla, CA, USA). Using docking data from the PyRx virtual screening tool, the degree of ligand interaction with the targeted protein's active site was determined, and 2D and 3D ligand-protein interaction images were taken using the visualizer software Pymol (version 2.5.5, Schrodinger Inc., New York, NY, USA) and BIOVIA Discovery Studio (version 21.1.0, Dassault, Systems, France).

ADME prediction

The SwissADME online platform (http://www.swissadme.ch/) was used for analysis to look at the physicochemical properties of effective candidates, such as aqueous solubility, lipid affinity, and pharmacokinetics. Adsorption, distribution, metabolism, and excretion (ADME) properties of LIN were predicted using the SwissADME online tool.

Results

In-vitro studies

Extraction

Our cold ethanol extraction (maceration) yielded 8 g of crude extract. Thus, the yield value was 1.6%.

Membrane-stabilizing capacity

The control vehicle showed a negligible membrane-protecting effect (1.34 ± 0.01%) on HRBCs. The extract ECS showed a significant ($p < 0.05$) and concentration-dependent membrane-lysing inhibitory effect in comparison to the control group. The highest inhibition (77.61 ± 0.01%) was seen by ECS at 160 µg/mL. However, the standard drug PPL exhibited significant ($p < 0.05$), strong, and better inhibition at 160 µg/ml (97.56 ± 0.01%) than the ECS at the same concentration. The IC_{50} values calculated for the PPL, ECS, and LIN were 54.13 ± 2.08, 17.92 ± 1.08, and 157.91 ± 1.88 µg/mL, respectively (Table 1). Additionally, we observed membrane-stabilizing activity of ECS and LIN using the membrane-stabilizing egg-albumin protein denaturation method. In this method, we observed that ECS and LIN demonstrated 27.62 ± 0.01 and 46.74 ± 0.02% membrane protection, while ASA showed 94.71 ± 0.01% at the maximum dose. The IC_{50} values of ASA, ECS, and LIN were 69.21 ± 2.03, 17.92 ± 1.08 µg/mL and 157.91 ± 1.88 µg/mL, respectively (Table 2).

Clot lysis test

The control vehicle exhibited negligible clot-lysing capacity (2.69 ± 0.02%). ECS exhibited mild but significant ($p < 0.05$) clot lysis capacity as compared to the control group. It showed a concentration-dependent clot lysis potential. At 160 µg, ECS exhibited the highest clot lysis (18.02 ± 3.968%). However, the standard SK (equiv. 30,000 IU)/100 µl exhibited more clot lysis capacity

Table 1 Membrane stabilizing capacity of *Coriandrum sativum* seed ethanol extract (ECS), LIN, PPL and control group using HRBC model

Sample/controls	Concentration	%Protection	IC_{50} [CI, R^2]
Control (Vehicle)	0.5 mL	1.34 ± 0.01	-
PPL	10 µg/mL	21.15 ± 0.01*	54.13 ± 2.08 µg/mL [36.59–61.19 µg/mL; 0.95]
	20 µg/mL	35.73 ± 0.01*	
	40 µg/mL	42.89 ± 0.01*	
	80 µg/mL	78.15 ± 0.01*	
	160 µg/mL	97.56 ± 0.01*	
ECS	10 µg/mL	40.78 ± 0.01*	17.92 ± 1.08 µg/mL [11.83–21.31 µg/mL; 0.85]
	20 µg/mL	59.19 ± 0.01*	
	40 µg/mL	67.09 ± 0.01*	
	80 µg/mL	69.72 ± 0.01*	
	160 µg/mL	77.61 ± 0.01*	
LIN	10 µg/mL	10.37 ± 0.01*	157.91 ± 1.88 µg/mL [141.87–201.33 µg/mL; 0.87]
	20 µg/mL	12.55 ± 0.01*	
	40 µg/mL	25.22 ± 0.01*	
	80 µg/mL	31.50 ± 0.01*	
	160 µg/mL	52.32 ± 0.01*	

Values are mean ± SD (standard deviation) ($n = 3$), One-way ANOVA followed by *t*-student post hoc test; *$p < 0.05$ when compared to the control (vehicle) group; ECS: Ethanolic extract of *Coriandrum sativum*; LIN: Linalool; PPL: Propranolol; IC_{50}: Half-minimum inhibitory concentration; CI: Confidence of interval; R^2: Co-efficient of determination

Table 2 Membrane stabilizing capacity of *Coriandrum sativum* seed ethanol extract (ECS), LIN, ASA and control group using egg-albumin protein denaturation model

Sample/controls	Concentration	%Protection	IC_{50} [CI, R^2]
Control (Vehicle)	0.5 mL	2.63 ± 0.01*	-
ASA	10 µg/mL	3.94 ± 0.02*	69.21 ± 2.03 µg/mL [53.81–73.33 µg/mL; 0.89]
	20 µg/mL	10.52 ± 0.01*	
	40 µg/mL	14.46 ± 0.01*	
	80 µg/mL	60.51 ± 0.04*	
	160 µg/mL	94.71 ± 0.01*	
ETA	10 µg/mL	5.26 ± 0.01*	310.23 ± 2.93 µg/mL [298.83–331.31 µg/mL; 0.85]
	20 µg/mL	13.15 ± 0.01*	
	40 µg/mL	19.73 ± 0.01*	
	80 µg/mL	21.04 ± 0.01*	
	160 µg/mL	27.62 ± 0.01*	
LIN	10 µg/mL	11.18 ± 0.01*	180.23 ± 1.98 µg/mL [163.79–183.31 µg/mL; 0.90]
	20 µg/mL	19.20 ± 0.01*	
	40 µg/mL	29.40 ± 0.01*	
	80 µg/mL	34.32 ± 0.01*	
	160 µg/mL	46.74 ± 0.02*	

Values are mean ± SD (standard deviation) ($n = 3$), One-way ANOVA followed by *t*-student post hoc test; *$p < 0.05$ when compared to the control (vehicle) group; ETA: Ethanol extract of *Trachyspermum ammi*; LIN: Linalool; ASA: Acetyl salicylic acid; IC_{50}: Half-minimum inhibitory concentration; CI: Confidence of interval; R^2: Co-efficient of determination

Table 3 Clot Lysis capacity of *Coriandrum sativum* seed ethanol extract, LIN, SK and control group

Sample/controls	Concentration	%Clot lysis	IC_{50} [CI, R^2]
Control (Vehicle)	100 µL	2.69 ± 0.02	-
SK (15,00,000 U/Vial/10 ml)	100 µL	78.49 ± 0.03*	-
ECS	10 µg/mL	8.95 ± 2.77*	333.33 ± 3.39 µg/mL [245.11–443.95 µg/mL; 0.86]
	20 µg/mL	11.35 ± 3.70*	
	40 µg/mL	14.64 ± 1.64*	
	80 µg/mL	17.73 ± 2.23*	
	160 µg/mL	18.02 ± 3.96*	
LIN	10 µg/mL	24.55 ± 0.33*	153.21 ± 1.09 µg/mL [141.10–173.97 µg/mL; 0.86]
	20 µg/mL	30.32 ± 1.02*	
	40 µg/mL	46.27 ± 0.86*	
	80 µg/mL	48.01 ± 0.55*	
	160 µg/mL	53.12 ± 1.59*	

Values are mean ± SD (standard deviation) ($n = 3$), One-way ANOVA followed by *t*-student post hoc test; *$p < 0.05$ when compared to the control (vehicle) group; ECS: Ethanolic extract of *Coriandrum sativum*; LIN: Linalool; SK: Streptokinase; IC_{50}: Half-minimum inhibitory concentration; CI: Confidence of interval; R^2: Co-efficient of determination

(78.49 ± 0.03) than the test samples. The IC_{50} values of ECS and LIN were 333.33 ± 3.39 and 153.21 ± 1.09 µg/mL, respectively (Table 3).

In-silico findings

Interaction of linalool with inflammatory mediators

LIN demonstrated significant binding affinity of -5.5, -4.6, -4.5, -4.6, -5.3, and – 4.4 kcal/mol with the inflammatory mediators COX-1, COX-2, NF-κB1, NF-κB2, TRPA1, and TRPV1, respectively. LIN and COX-1 binding interactions were formed with 9 alkyl and 3 p-alkyl residues of the COX-1 receptor. In the case of the LIN and COX-2 binding interaction, we found two conventional hydrogen bonds with YR113 and GLY114, and 3 alkyl and 4 p-alkyl residues of the COX-2 protein. LIN is bound through one conventional hydrogen bond with the PHE113 residue and seven alkyl bonds of the NFKB1 receptor. Further, we observed the binding interaction of LIN and NFKB2, where there was one conventional hydrogen bond with the ARG193 residue and several alkyl bonds with the ALA104, LYS153, ILE119, and LEU117 residues. LIN also showed binding interaction with TRPA1 through twelve conventional bonds with LEU186, LEU188, ILE281, TYR102, HIS199, PHE207, and TRP296 residues. One carbon-hydrogen bond with ASN30, one alkyl bond with VAL295, and one pi-sigma and one pi-alkyl bond with PHE305 were observed in the LIN and TRPV1 binding interactions. (Table 4, and Figs. 1 and 2, and 3).

Interaction of linalool with tPA and uPA

In our in-silico studies, LIN also exhibited significant binding affinity of -5.2 and – 4.4 Kcal/mol with tPA and uPA, respectively. We found that LIN was bound with tPA through an alkyl bond with several residues,

Table 4 Binding interaction of linalool and inflammatory mediators

Protein (Receptor)	Binding affinity (Kcal/mol)	Amino acid residues	Types	Bond length (Å)
COX-1	-5.3	VAL58	Alkyl	4.10731
		ALA62	Alkyl	3.58722
		ILE37	Alkyl	5.38391
		VAL374	Alkyl	4.78049
		ILE37	Alkyl	4.09361
		VAL58	Alkyl	4.92748
		VAL58	Alkyl	4.56704
		ARG438	Alkyl	4.36782
		ARG439	Alkyl	4.11352
		HIS61	Pi-Alkyl	4.94063
		TYR371	Pi-Alkyl	4.62628
		PHE377	Pi-Alkyl	5.02433
		HIS378	Pi-Alkyl	4.73068
COX-2	-4.6	YR113	Conventional H-Bond	1.98019
		GLY114	Conventional H-Bond	2.29319
		PRO223	Alkyl	4.18647
		LEU95	Alkyl	5.16894
		PRO223	Alkyl	4.23856
		PRO223	Alkyl	4.22933
		TYR110	Pi-Alkyl	5.02457
		TYR110	Pi-Alkyl	5.08076
		PHE219	Pi-Alkyl	4.48998
		PHE219	Pi-Alkyl	4.61623
NF-κB1	-4.5	PHE113	Pi-Donor H-Bond	3.10463
		ALA102	Alkyl	3.82693
		LYS93	Alkyl	4.53123
		VAL72	Alkyl	4.82418
		TYR100	Pi-Alkyl	5.02056
		TYR100	Pi-Alkyl	5.48792
		HIS111	Pi-Alkyl	5.0211
		PHE113	Pi-Alkyl	5.04173
NF-κB2	-4.6	ARG193	Conventional H- Bond	2.56761
		ALA104	Alkyl	4.31215
		ALA104	Alkyl	3.73859
		LYS153	Alkyl	5.10637
		ILE119	Alkyl	4.69229
		LEU117	Alkyl	3.88851
		LYS153	Alkyl	3.5462
		LYS153	Alkyl	4.2274
TRPA1	-5.2	LEU186	Alkyl	5.45549
		LEU188	Alkyl	4.89489
		LEU188	Alkyl	5.43779
		LEU188	Alkyl	4.27333
		ILE281	Alkyl	4.44379
		TYR102	Pi-Alkyl	4.5157
		TYR102	Pi-Alkyl	4.31726
		HIS199	Pi-Alkyl	4.00478
		PHE207	Pi-Alkyl	4.92402
		PHE207	Pi-Alkyl	5.33855
		TRP296	Pi-Alkyl	5.25798
		TRP296	Pi-Alkyl	5.31036
TRPV1	-4.4	ASN30	Carbon Hydrogen Bond	3.46894
		PHE305	Pi-Sigma	3.8235
		VAL295	Alkyl	4.127
		PHE305	Pi-Alkyl	4.94689

including VAL210, LEU128, LEU130, LEU162, LEU181, and LYS230. We also observed two conventional hydrogen bonds with ARG239 and THR24, seven alkyl bonds with ARG239, LEU123, ILE238, and MET47 of uPA in LIN and uPA binding interaction (Table 5; Fig. 4).

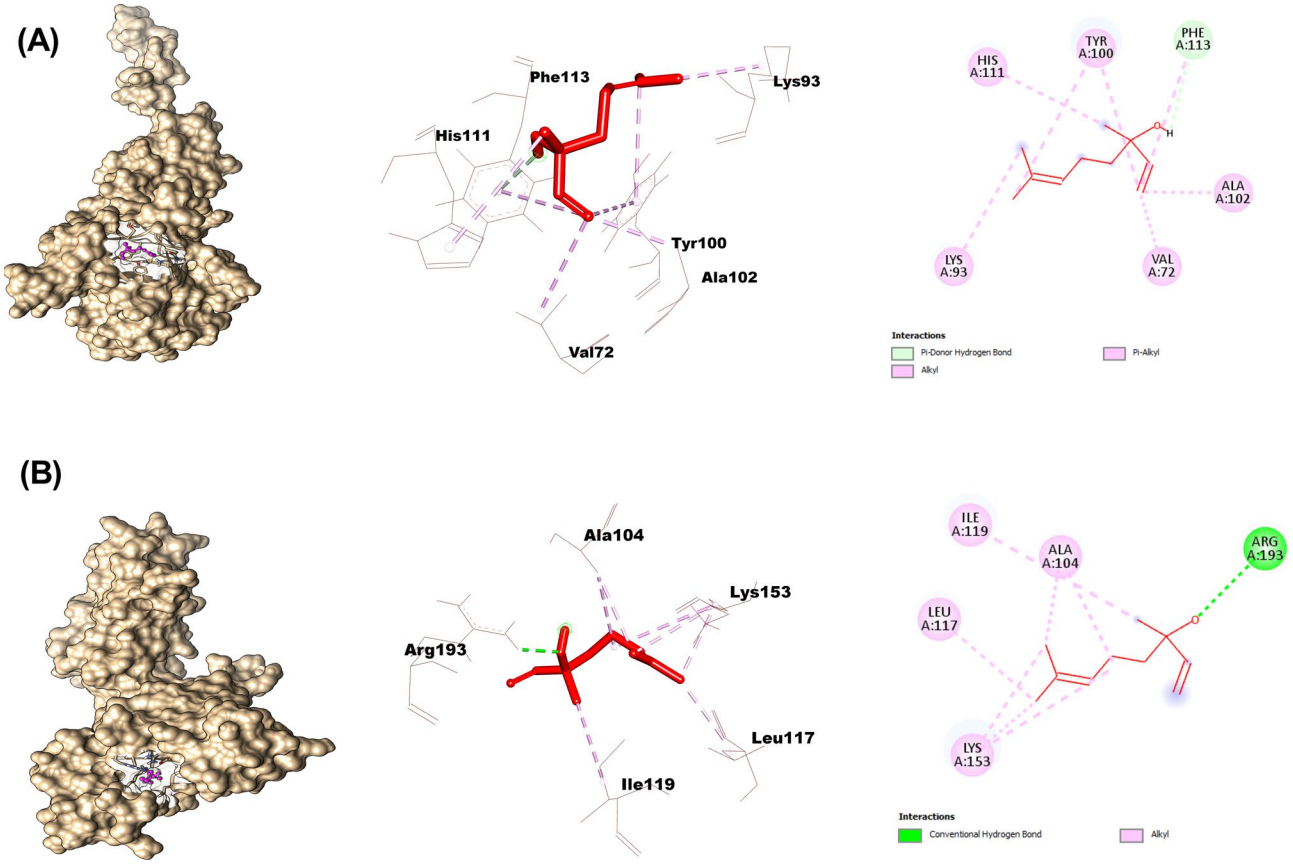


Fig. 1 Binding interaction of linalool with NF-κB1 and NF-κB2. [(**A**) 3D and 2D binding interaction of linalool and NF-κB1. (**B**) 3D and 2D binding interaction of Linalool and NF-κB2]

Pharmacokinetics and drug-likeness properties

According to the in-silico analysis, we utilized the SwissADME online tool to examine the absorption, distribution, metabolism, and excretion (ADME) profile and drug-likeness features of LIN, as illustrated in Fig. 5 and summarized in Table 6. This section lists basic physicochemical and molecular properties such as molecular refractivity (MR), molecular weight (MW), the sum of exact atom types, polar surface area (PSA), and the number of heavy atoms, aromatic heavy atoms, H-bond acceptors (HBAs), and H-bond donors (HBAs) (HBDs).

The partition coefficient between n-octanol and water (log Po/w) is recognized as a standard descriptor in lipophilicity for pharmacokinetic drug design and discovery [35]. SwissADME provides five lipophilicity prediction models, one of which is an atomistic approach with correction factors and a knowledge-based repository [36]. Water solubility is a unique property used in medication manufacture that influences absorption and provides the appropriate amount of active ingredients in a restricted number of therapeutic dosages [37]. The ESOL model is a water solubility prediction method that SwissADME may employ. In terms of bioavailability, the drug-likeness feature is a major factor in predicting the possibility that a molecule may develop an oral therapeutic [38]. SwissADME provides several criteria that classify the molecule as drug-like by applying the rule-based Ghose method. The outcomes satisfy all the necessary requirements for the pharmacokinetic, physicochemical, and drug-like characteristics of powerful hits when taken orally [39]. The results in Fig. 5; Table 6 indicated that LIN was water-soluble and met Lipinski's requirements. Their synthetic accessibility was likewise equivalent to the norm, and its high gastrointestinal absorption (GIA) showed that it was well absorbed orally.

Discussion

In this study, we prepared *C. sativum* extract in ethanol. It is because ethanol is widely used to prepare crude extract or their fractions from varieties of test samples, including medicinal plants. Ethanol has high polarity among the other organic solvents; therefore, it has the capability to dissolve polar bioactive compounds in crude extracts. Additionally, it can protect extract from microbial attack [40]. Our study aims to explore alternative drugs for membrane stabilization and clot lysis, and our experimental findings suggest that *C. sativum*, along with its major component LIN found in the essential oil,

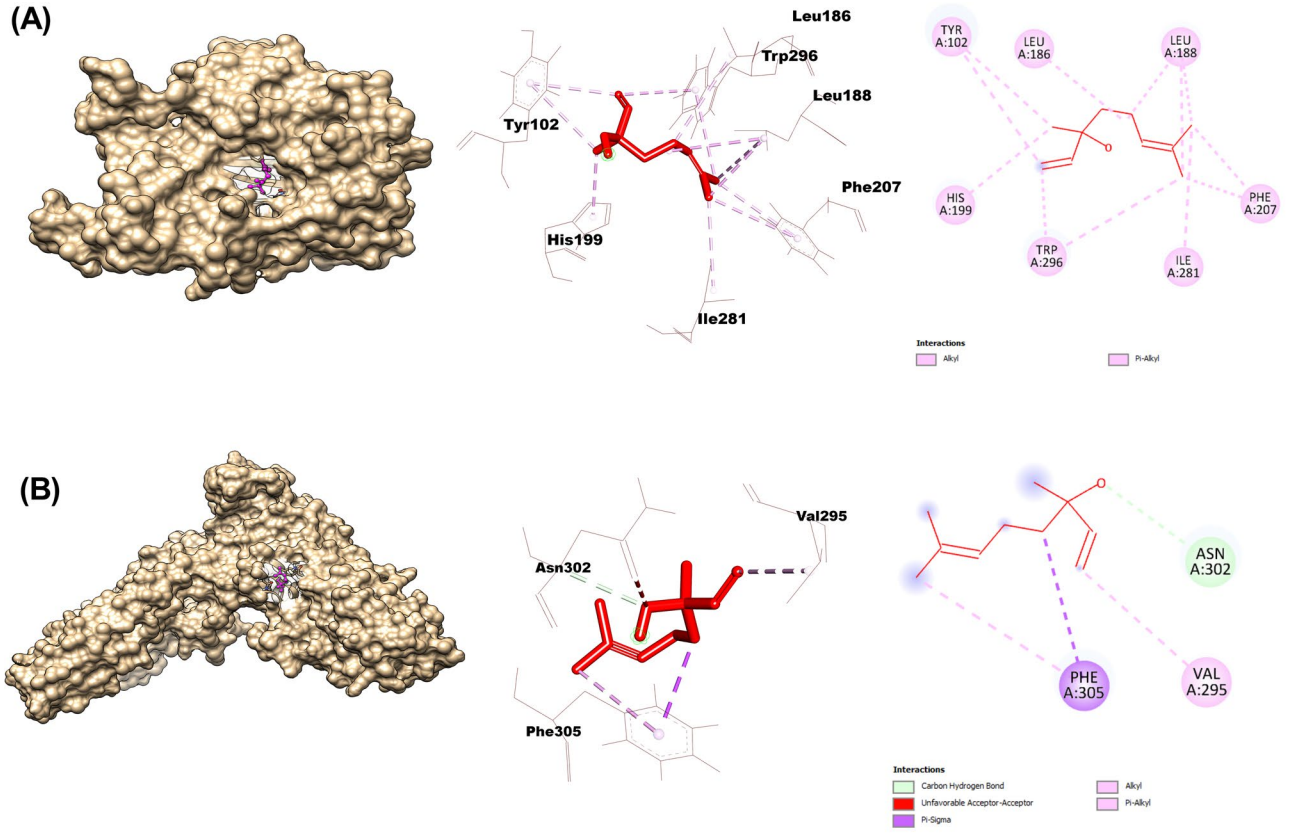


Fig. 2 Binding interaction of linalool with TRPA1 and TRPV1. [(**A**) 3D and 2D binding interaction of linalool and TRPA1. (**B**) 3D and 2D binding interaction of Linalool and TRPV1]

may serve as a promising treatment option. Both substances are known for their anti-inflammatory and antioxidant properties, which could contribute to membrane stabilization.

Inflammation plays an important role in our body [41]. However, chronic inflammation is linked with many pathological phenomena, including aging, metabolic diseases and disorders (diabetes, cardiovascular diseases), and cancer [42]. A membrane-stabilizing test is performed to check the anti-inflammatory capacity of diverse biological and chemical samples, including plant extracts and their derived components [43]. In this bioassay, erythrocytes are exposed to hypotonic solution to induce their membrane lysis [44]. Thus, a sample having membrane-protecting capacity should inhibit membrane lysis, thereby inhibiting leakage of serum protein and fluids from the erythrocytes [32, 45]. Certain drugs can promote RBC lysis, which is a major consequence of drug-induced immune hemolytic anemia (DIIHA), for example, cefotetan, ceftriaxone, and piperacillin [46]. It happens when these drugs induce certain antibodies that cause sensitization of the RBC cell membrane with or without fixation of complement, leading to the lysis of RBCs and the release of their contents in the plasma [47]. In this study, we have seen that ECS concentration-dependently inhibited membrane lysis of RBCs, indicating its membrane-protecting power. One study reported that *C. sativum* has immunomodulatory effects, where the authors demonstrated that this herb can inhibit inducible nitric oxide synthase (iNOS) expression, thereby inhibiting the production of reactive oxygen and nitrogen species (i.e., ROS and RNS) [48]. In another study, Kothari et al. [49] reported that a dichloromethane extract of *C. sativum* showed membrane-stabilizing activity of 63.39% at 1000 µg. In this study, ECS exhibited the highest membrane-protecting capacity by 77.61 ± 0.01% at 160 µg/m. Zeb [10] reported that the ethanol extract of *C. sativum* contains a high amount of LIN, about 57.5–75.1% in concentration. Several studies indicate that *C. sativum* is rich with essential oils, fatty acids, and terpenes (e.g., monoterpenes, sesquiterpenes) [50]. Essential oils are protective in nature. It is due to their strong antioxidant and anti-inflammatory capacity [51, 52].

Linalool (LIN), in particular, has demonstrated anti-inflammatory, anticoagulant, and fibrinolytic activities in some studies, suggesting its potential role in inflammation and clot lysis [53]. The mechanisms underlying LIN's anti-inflammatory and clot-lysing activities are complex and involve interactions with various cellular

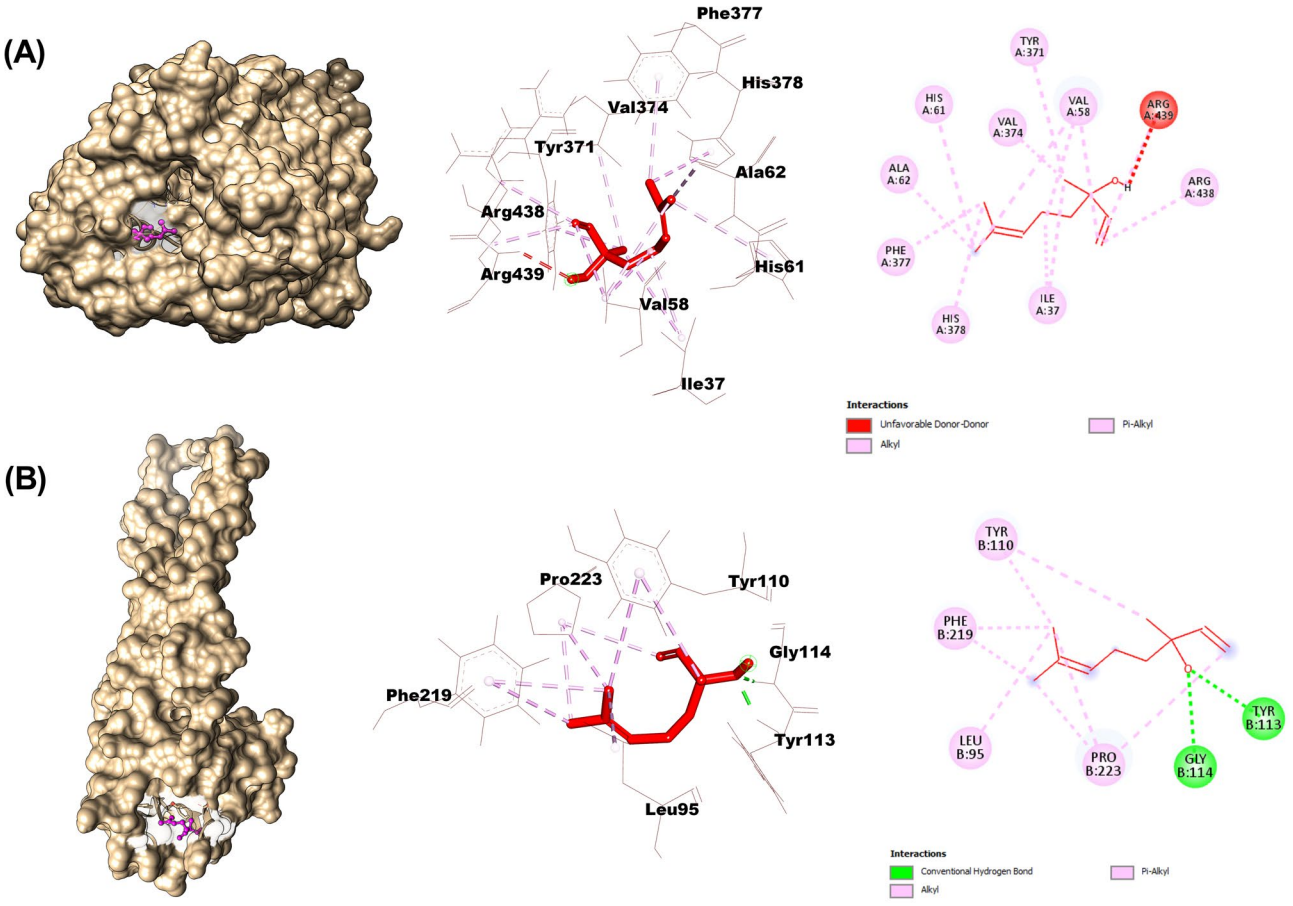


Fig. 3 Binding interaction of linalool with COX-1 and COX-2. [(**A**) 3D and 2D binding interaction of linalool and COX-1. (**B**) 3D and 2D binding interaction of Linalool and COX-2]

Table 5 Interaction of LIN with tPA and uPA

Protein (Receptor)	Binding affinity (Kcal/mol)	Amino acid residues	Types	Bond ength (Å)
tPA	-5.2	VAL210	Alkyl	5.00004
		LEU128	Alkyl	4.73344
		VAL210	Alkyl	3.94163
		LEU130	Alkyl	4.66233
		LEU162	Alkyl	5.09453
		LEU181	Alkyl	5.15931
		LEU162	Alkyl	4.83486
		LEU162	Alkyl	3.66995
		LEU181	Alkyl	4.05823
		LEU181	Alkyl	5.18874
		LYS230	Alkyl	4.18315
uPA	-4.4	ARG239	Conventional H- Bond	2.90834
		THR24	Conventional H-Bond	1.90123
		ARG239 ARG239	Alkyl	4.58734
		LEU123	Alkyl	3.9978
		ILE238	Alkyl	5.4041
		MET47	Alkyl	5.17877
		LEU123	Alkyl	4.81552
		LEU123	Alkyl	4.6158
			Alkyl	4.83752

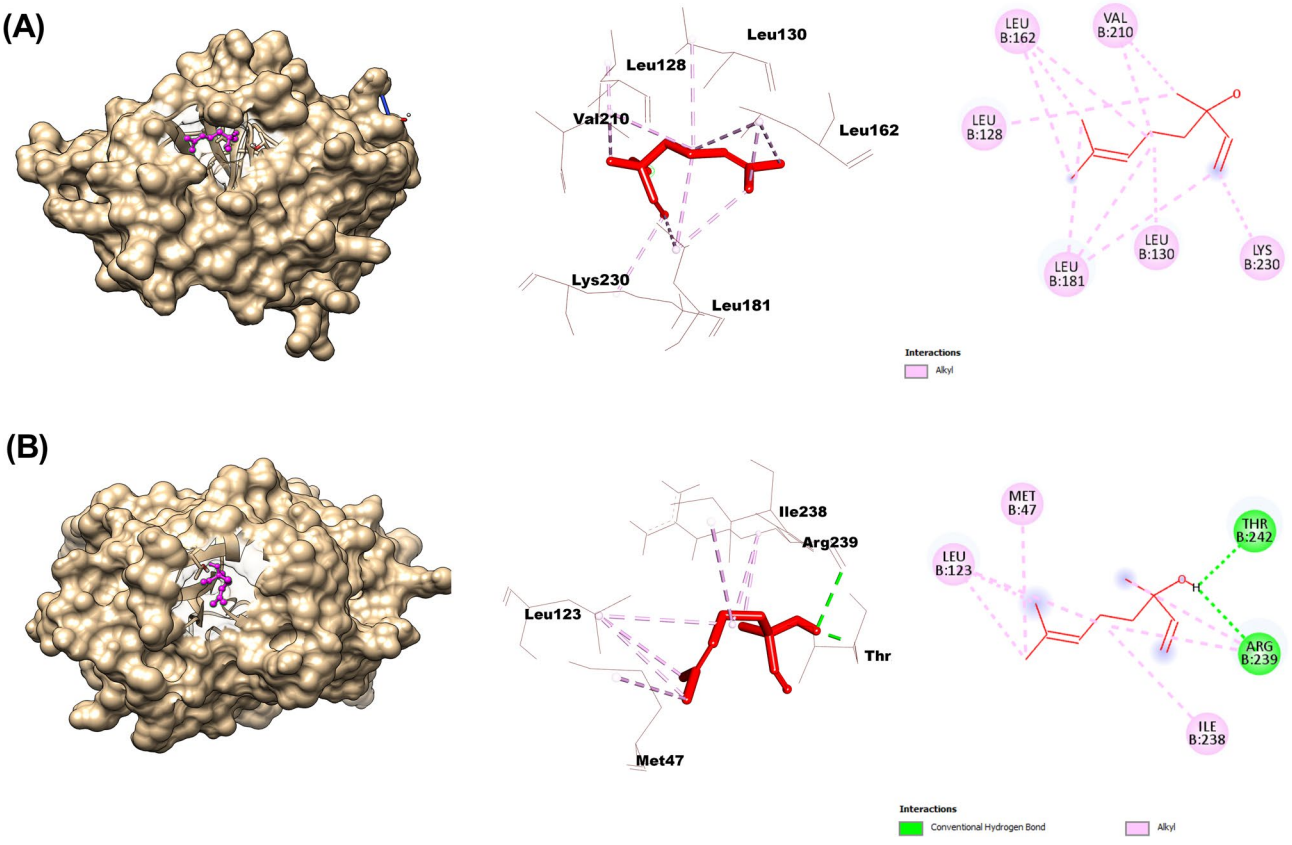


Fig. 4 Binding interaction of linalool with tPA and uPA. [(**A**) 3D and 2D binding interaction of linalool and tPA. (**B**) 3D and 2D binding interaction of Linalool and uPA]

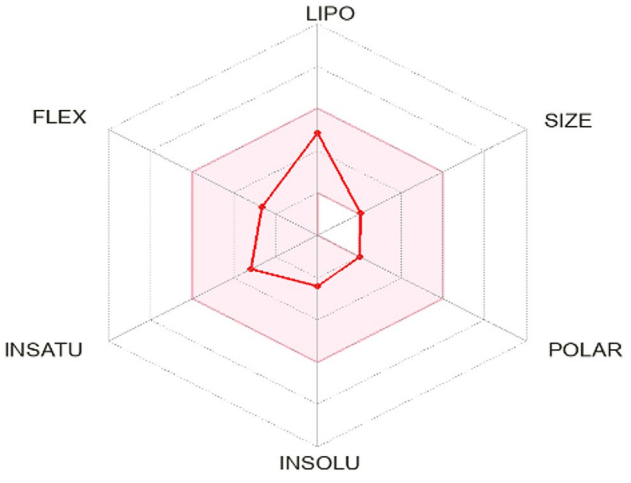


Fig. 5 ADME properties of linalool generated by the SwissADME. [The colored zone is the suitable physicochemical space for oral bioavailability. LIPO (Lipophilicity): -0.7 < XLOGP3 < + 5.0; SIZE: 150 g/mol < MV < 500 g/mol; POLAR (Polarity): 20 $Å^2$ < TPSA < 130 $Å^2$; INSOLU (Insolubility): -6 < Log S (ESOL) < 0; INSATU (Insaturation): 0.25 < Fraction Csp 3 < 1; FLEX (Flexibility): 0 < NUM. rotatable bonds < 9]

Table 6 Pharmacokinetic and drug-likeness properties of Linalool

Properties	Factors	Linalool
Physico-chemical Properties	Formula	C10H18O
	MW (g mol^{-1})	154.25
	Heavy atoms	11
	H-Bond donors (HBDs)	1
	H-Bond acceptors (HBAs)	1
	Molar refractivity	50.44
	Topological polar surface area (TPSA)($Å^2$)	20.23
Lipophilicity	Consensus Log $P_{o/w}$	2.66
Water solubility	Log S (ESOL)	-2.40
Pharmacokinetics	GI absorption	High
Drug likeness	Lipinski	Yes; 0 violation
	Bioavailability Score	0.55
Medicinal Chemistry	Synthetic accessibility	2.74

and molecular targets. Our study demonstrated that ECS and LIN exhibited significant clot lysis activity compared to the control group. Studies have demonstrated its influence on enzymes involved in clot formation and dissolution, as well as its ability to modulate immune cell responses [54]. LIN's anti-inflammatory properties are

believed to involve its interaction with several molecular targets, including receptors associated with the inflammatory response [55]. One notable target is the transient receptor potential (TRP) channels, specifically TRPA1 and TRPV1 [56]. TNF-α (tumor necrosis factor-alpha), RANTES (regulated on activation, normal T cell expressed and secreted), and MCP-1 (monocyte chemoattractant protein-1) are the three pro-inflammatory cytokines that promote inflammation in the body [57]. LIN possibly works on these cytokines to modulate inflammation [58]. LIN demonstrates anti-inflammatory effects in BV2 microglial cells subjected to lipopolysaccharide (LPS)-induced inflammatory responses [59]. LIN also shows promising activity to reduce atherosclerosis [60]. Research suggests that LIN exhibits anti-inflammatory effects by modulating various pathways in the body [61]. LIN has been found to inhibit pro-inflammatory molecules, such as cytokines and chemokines, thereby reducing the inflammatory response, and it suppresses cisplatin-induced NF-κB (nuclear factor kappa light chain B) activation in a dose-dependent manner [62]. This property makes LIN a potential candidate for managing inflammatory conditions [63]. Moreover, LIN has shown promising clot lysis activity, a critical process in preventing and treating thrombotic events [53]. Thrombosis, the formation of blood clots, can lead to serious conditions like heart attacks and strokes [64]. LIN has been investigated for its ability to interfere with the clotting cascade, promoting fibrinolysis—the dissolution of blood clots [53]. By enhancing clot lysis, LIN may contribute to preventing excessive clot formation and reducing the risk of thrombotic events [65]. Our in-vitro study demonstrated that LIN demonstrated dose-dependently significant membrane protection and clot lysis activity compared to the control group. In further in-silico studies, we observed that LIN showed efficient binding affinity with inflammatory mediators including COX-1, COX-2, NF-κB1, NF-κB2, TRPA1, and TRPV1, and clot lysis factors tPA and uPA. Previous studies demonstrate that *C. sativum* has membrane-protecting and anti-atherothrombotic capacity [66]. Therefore, our findings are an agreement with previous studies.

In membrane stabilization and anti-inflammatory studies, we have seen that the standard drugs PPL and ASA exhibited IC_{50} values of 54.13 ± 2.08 and 69.21 ± 2.03 µg/mL, respectively, which follow clinically usable doses of these drugs in humans. For example, ASA is commonly used as an anti-inflammatory drug at 75 mg/day, while PPL is at 80 mg/day. The potential therapeutic effects of *C. sativum* with its major ingredient, LIN, observed in our experiments, indicate that these natural compounds could be considered as alternatives in the development of drugs targeting inflammation and clot lysis. Further research, including clinical trials, is warranted to validate these initial findings and assess the safety and efficacy of *C. sativum* and LIN as potential drugs for these medical applications. If confirmed, these natural compounds could offer novel and potentially accessible treatment options in the field of cardiovascular health. Thus, our findings are in agreement with the previous studies.

Conclusion

ECS exhibited significant membrane-stabilizing capacity in a concentration-dependent manner. It also showed a significant ($p < 0.05$) clot lysis capacity concentration-dependently. It showed strong membrane-stabilizing but mild clot-lysing capacity in comparison to the control groups. It may be possible due to the presence of LIN. Thus, LIN also exhibited significant membrane-stabilizing and clot lysis activity in our in-vitro studies and significant binding affinity with inflammatory mediators and clot lysis factors in our in-silico studies. ECS or its major compound, LIN, might be a good candidate for the treatment of inflammatory diseases. Further studies are necessary to isolate its bioactive principles and elucidate molecular mechanisms for membrane-stabilizing activity. However, we didn't perform in-vivo studies and didn't check inflammatory marker expression profile in this study; more studies are highly appreciated to confirm our in-vitro and in-silico-based findings.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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