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Original Article

Molecular Docking Study of *Ageratum conyzoides*-Derived Compounds Against the Human Cathepsin G–EapH1 Complex of *Staphylococcus aureus*

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Abstract
Under normal physiological conditions, neutrophils circulate throughout the bloodstream in a resting or quiescent state. However, following activation and the phagocytic uptake of opsonized bacterial pathogens, these cells experience substantial functional and physiological alterations that enhance their antimicrobial capabilities. *Ageratum conyzoides* is a medicinal plant reported to possess antimicrobial activity due to the presence of several bioactive phytochemicals. These compounds may serve as potential candidates for inhibiting bacterial virulence proteins. In addition to having a variety of beneficial biological activities, this compound also has some weaknesses. One of its main weaknesses is its low solubility in water, which can inhibit its bioavailability when consumed. Therefore, molecular docking of the compound Bandotan derivatives was carried out to address these weaknesses. The purpose of this study is to analyze the interaction of the Bandotan compound with the Human Cathepsin-G Inhibited by *S. aureus* Eaph1 receptor (6VTM); Molecular docking was performed using AutoDockTools 1.5.7, while the absorption, distribution, metabolism, and excretion properties of the compounds were predicted using the pkCSM web server, and their toxicity was evaluated using the ProTox-II web server. The ligand–receptor interactions were visualized using BIOVIA Discovery Studio Visualizer. All compounds derived from *Ageratum conyzoides* were able to interact with the human cathepsin G–EapH1 complex of *S. aureus* (PDB ID: 6VTM). Sesamin exhibited the most favorable binding energy of −6.21 kcal/mol, with an estimated inhibition constant (Ki) of 28.22 µM. The compound interacted with Arg977, Asp974, Pro975, Ile981, Asp984, Val980, Gly983, Gln976, Leu979, Glu985, and Gln982 through hydrogen bonds and other noncovalent interactions. Overall, sesamin demonstrated the best docking performance among the evaluated compounds and was identified as the most promising *A. conyzoides*-derived compound for interaction with the human cathepsin G–EapH1 complex.

Keywords: Bandotan; anti-microbial; Eaph1; Interaction; Molecular docking.

INTRODUCTION

Infections caused by *Staphylococcus aureus* remain one of the leading causes of skin and soft tissue infections, as well as systemic infections worldwide. This bacterium possesses various virulence factors that enable colonization, tissue invasion, and evasion of host immune responses, allowing it to cause a wide spectrum of diseases ranging from mild infections to life-threatening conditions. The increasing prevalence of antibiotic-resistant strains, particularly *Methicillin-resistant Staphylococcus aureus* (MRSA), has become a major challenge in infection control and the development of novel antimicrobial therapies. The ability of *S. aureus* to establish infection is influenced not only by its capacity to adapt to antibiotic pressure but also by its interactions with the host immune system, especially neutrophils,

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which serve as key components of innate immune defense. Neutrophils play a crucial role in recognizing, phagocytosing, and destroying bacteria through the release of antimicrobial granules, the production of reactive oxygen species (ROS), and the formation of neutrophil extracellular traps (NETs), which help restrict the spread and facilitate the elimination of pathogens (Herro & Grimes, 2024). Upon exposure to opsonized bacteria, neutrophils become activated and undergo a series of functional changes, including phagosome formation, granule-phagosome fusion, NADPH oxidase-mediated respiratory burst, and intracellular microbial killing (Naish et al., 2023). Furthermore, neutrophils contribute to immune regulation through the secretion of cytokines and chemokines and through interactions with various immune cells, thereby coordinating both innate and adaptive immune responses against *S. aureus* infection (Shafqat et al., 2023).

One of the virulence mechanisms employed by *Staphylococcus aureus* is the production of Extracellular adherence protein homolog 1 (EapH1), a secreted protein that functions as a potent inhibitor of Human Cathepsin G (CG), a neutrophil serine protease that plays a critical role in innate immune defense. Cathepsin G belongs to the family of neutrophil serine proteases (NSPs), which are stored within azurophilic granules and contribute to host protection through antimicrobial activity and regulation of inflammatory responses (Korkmaz et al., 2010). Along with neutrophil elastase (NE), proteinase 3 (PR3), and neutrophil serine protease-4 (NSP4), Cathepsin G forms part of a highly conserved group of proteases that exhibit similar three-dimensional structures despite differences in substrate specificity (Perera et al., 2012; Fujinaga et al., 1996). These proteases are involved in the degradation of engulfed microorganisms within phagolysosomes and contribute to immune regulation through the proteolytic modification of cytokines, chemokines, membrane receptors, and extracellular matrix components (Soehnlein & Lindbom, 2010; Pham, 2006). Structural and evolutionary analyses have demonstrated that Cathepsin G shares a conserved chymotrypsin-like fold and catalytic machinery with other NSP family members, reflecting their common evolutionary origin and specialized roles in antimicrobial defense (Schuhmann et al., 2022). Furthermore, Cathepsin G is synthesized as an inactive precursor and undergoes proteolytic activation before exerting its biological functions, a mechanism conserved among neutrophil serine proteases (Chitsamankhun et al., 2024). By producing EapH1, *S. aureus* is able to inhibit the proteolytic activity of Cathepsin G, thereby impairing one of the host's key antimicrobial defense mechanisms. This inhibition facilitates bacterial survival and immune evasion by reducing neutrophil-mediated pathogen killing, ultimately enhancing the ability of *S. aureus* to persist within the host and establish infection (Cheetham et al., 2024).

Current treatment of *Staphylococcus aureus* infections remains largely dependent on the use of antibiotics. However, the increasing emergence and spread of antibiotic-resistant strains have significantly reduced the effectiveness of conventional antimicrobial therapies, posing a major challenge to infection management. As a result, there is an urgent need to identify and develop novel therapeutic agents that can overcome bacterial resistance and improve treatment outcomes. One promising strategy involves

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targeting bacterial virulence factors rather than directly inhibiting bacterial growth, thereby reducing the selective pressure that drives the development of antibiotic resistance. In particular, the inhibition of virulence-associated proteins that enable immune evasion and host colonization has gained considerable attention as an alternative antimicrobial approach. Therefore, the discovery of new bioactive compounds capable of interfering with bacterial virulence mechanisms represents an important direction for the development of next-generation anti-*S. aureus* therapies (Okunade, 2002; Van Wyk & Wink, 2017).

Ageratum conyzoides L. is a medicinal plant that has been widely used in traditional medicine and has attracted considerable scientific interest due to its diverse biological activities. Among its reported pharmacological properties, antimicrobial activity has received particular attention, as numerous studies have demonstrated its effectiveness against a variety of pathogenic microorganisms (Yadav et al., 2019; Kotta et al., 2020). The antimicrobial potential of *A. conyzoides* is believed to be associated with its rich phytochemical composition. Phytochemical investigations have revealed the presence of various bioactive secondary metabolites, including flavonoids, chromenes, terpenoids, sterols, and pyrrolizidine alkaloids, many of which have been reported to possess antimicrobial and other biologically relevant activities (Okunade, 2002). In particular, flavonoids and chromene derivatives are considered important contributors to the biological properties of the plant due to their ability to interact with microbial targets and modulate cellular processes. The diversity of these phytochemical constituents suggests that *A. conyzoides* may serve as a promising natural source of bioactive compounds for the development of alternative antimicrobial agents and anti-virulence therapeutics (Yadav et al., 2019; Kotta et al., 2020; Okunade, 2002).

Molecular docking is a widely used Computer-Aided Drug Design (CADD) approach for predicting the binding affinity and interaction patterns between ligands and target proteins in a rapid and cost-effective manner prior to *in vitro* and *in vivo* investigations. This computational technique enables the evaluation of ligand–protein interactions at the molecular level and provides insights into the binding modes that may contribute to the inhibition or modulation of target protein activity. Consequently, molecular docking has become an important tool in drug discovery and development, facilitating the identification and optimization of potential therapeutic compounds while reducing the time and resources required for experimental screening (Agu et al., 2023; Sethi et al., 2019).

To date, no study has systematically evaluated the interactions of multiple major compounds from *Ageratum conyzoides* with the Human Cathepsin G–EapH1 complex using molecular docking combined with ADMET and toxicity predictions. Therefore, this study was conducted to address this research gap and provide further insight into the potential of *A. conyzoides* compounds as anti-virulence agents.

Based on the aforementioned background, this study aims to evaluate the potential of bioactive compounds from *Ageratum conyzoides* as candidate inhibitors of the Human Cathepsin G–EapH1 complex using molecular docking, as well as pharmacokinetic and toxicity predictions.

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METHODS

This study employs a molecular docking process of derivative compounds from Bandotan against the Human Cathepsin-G Inhibited by *S. aureus* Eaph1 receptor (6VTM) using the Discovery Studio and AutodockTools applications.

The tools used in this study include, AutodockTools (ADT) version 1.5.7, ChemDraw, and Discovery Studio (DS) 2021. The database sources employed are PubChem, Protein Data Bank, KNApSAck, PKCSM, and ProTox Prediction Webserver.

The materials used in this research include the 3D and 2D structures of derivative compounds found in *Bandotan* herb, a control ligand (N[3({2[(1methyl1Hpyrazol4yl)amino]7H pyrrolo[2,3d]pyrimidin4yl}oxy)phenyl]pro penamie), the drug compound , and the target receptor (macromolecule) Human Cathepsin-G Inhibited by *S. aureus* Eaph1 receptor with PDB ID 6VTM and a resolution of 1.60 Å.

Prediction of Lipinski Rule of Five, ADME, and Toxicity

The drug-likeness and pharmacokinetic characteristics of the compounds were assessed through Lipinski's Rule of Five and ADME (absorption, distribution, metabolism, and excretion) analyses using the pkCSM web platform. In addition, the potential toxicological profiles of the compounds were evaluated with the aid of the ProTox web server, which provides computational toxicity predictions.

Downloading Ligands and Receptors

The molecular structures of the selected compounds, including both their 3D and 2D conformations, were sourced from the PubChem database and downloaded in SDF format for subsequent analysis. In parallel, the target protein serving as the macromolecular receptor was acquired from the Protein Data Bank (PDB), where it was obtained in the conventional PDB file format required for molecular docking studies.

Ligand and Protein Preparation

The ligand compounds downloaded from PubChem were opened in ChemDraw to create 2D structures and saved as *.mol files. These files were then opened in Chem3D, where energy minimization was performed and saved as *.pdb files. The ligands were further prepared using AutodockTools through steps such as hydrogen addition, non-polar merging, Gasteiger charge addition, and setting torsion counts.

Protein (macromolecule) preparation involved importing the PDB-formatted protein into Discovery Studio. The protein was separated from other compounds not part of the active site and saved again in PDB format. The preparation was continued using AutodockTools, where polar hydrogens were added to the receptor and saved in *.pdbqt format for further processing.

Validation of Docking Method (Redocking)

Docking method validation was performed through redocking, where the natural ligand was re-docked onto the receptor using AutoDockTools. Ligand *.pdbqt files were configured with a grid

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box to ensure the ligand fit into the box and saved as *.gpf files.

Molecular Docking Process

As with method validation, the molecular docking process was conducted by preparing the ligands using AutodockTools (ADT). The Lamarckian Genetic Algorithm value was set to 100. The molecular docking process using AutodockTools (ADT) was executed via the command prompt with appropriate parameters.

Interaction Visualization

Visualization was conducted using AutodockTools (ADT) and Discovery Studio (DS) software to evaluate the compatibility of shape and volume between the ligand and the binding site.

RESULTS

Prediction of Lipinski's Rule of Five

Drug-likeness assessment was conducted based on several key physicochemical parameters widely recognized in the evaluation of potential oral drug candidates. The assessment parameters require candidate compounds to possess a molecular mass of less than 500 Da, contain no more than five hydrogen bond-donating groups, have a maximum of ten hydrogen bond-accepting groups, and exhibit a partition coefficient (log P) value that does not exceed five (Saxena et al., 2019). As presented in Table 1, all analyzed compounds comply with these requirements, indicating favorable physicochemical characteristics and suggesting their suitability for development as orally administered therapeutic agents.

Table 1. Analysis Results of Lipinski's Rule of Five for Ligand Compounds

Active Compound	MW	Log P	HBA	HBD
Sesamin	354.11	4.02	3	1
Nobiletin	402.13	2.2	5	2
Beta-Stigmasterol	412.37	2.99	4	2
Linderoflavone B	386.10	1.85	8	4
Ageconyflavone A	356.08	2.77	4	2

Source: Primary data, 2024

Prediction Results of ADME and Toxicity

The prediction of ADME values and toxicity is crucial based on five criteria: absorption (A), distribution (D), metabolism (M), excretion (E), and toxicity (T).

The data results show that the intestinal absorption of the five compounds exceeds 80%, and their skin permeability values have a logKp greater than -2.5 cm/hour. The compounds Sesamin and Nobiletin have low DVss values of -0.101 and -0.121, respectively. The compounds Beta-Stigmasterol, Linderoflavone B, and Agenconyflavone A have logBB values greater than 0.3.

Regarding toxicity classes, the compound Ageconyflavone A falls under class 1; Nobiletin and Sesamin fall under class 2; Beta-Stigmasterol falls under class Linderoflavone falls under class 6.

Results of Downloading, Ligand, and Receptor Preparation

The ligand was prepared by drawing its structure in 2D format using the ChemDraw application, which was then converted into a 3D format using Chem3D. The results of the 2D and 3D structure preparations of the ligand are listed in Table 2.

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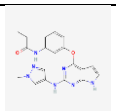
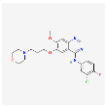
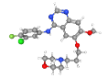
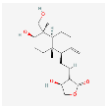
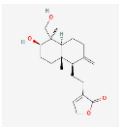
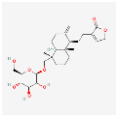
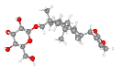
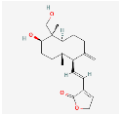
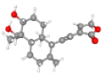
Table 2. Results of Downloading, Ligand, and Receptor Preparation

No	Ligand Name	2D Structure	3D Structure
1	Sesamin		
2	Nobiletin		
3	*Beta-Stigmasterol*		
4	*Linderoflavone*		
5	*Ageconyflavone*		
6	*5,6,7,3'-Tetramethoxy-4', 5'-methylenedioxyflavone*		
7	*4'-Hydroxy-5,6,7,3',5'-penthamethoxyflavone Ageconyflavone C 2-(4-Hydroxy-3,5-dimethoxyphenyl)-5,6,7-trimethoxy-4H-1-benzopyran-4-one*		

Source: Primary data, 2024

The target receptor (macromolecule) used in this study is Human Cathepsin-G Inhibited by *S. aureus* Eaph1 receptor with PDB ID 6VTM and a resolution of 1.60 Å, which was downloaded from the online Protein Data Bank (PDB).

Validation Results of the Method / Redocking

Validation of the molecular docking protocol was carried out using MGL Tools 1.5.6 integrated with AutoDock Tools 4.2. The reliability and accuracy of the docking procedure were confirmed based on the root mean square deviation (RMSD) value, where a result below 2 Å indicates that the method is sufficiently valid and suitable for subsequent docking analyses (Ramadhan *et al*., 2020). Validation data of the Human Cathepsin-G Inhibited by *S. aureus* Eaph1 receptor method with the control ligand is presented in Table 3.

Table 3. Validation Results of the Control Ligand on the Active Site of Eaph1

No	Compound Name	RMSD	ΔG	KI	H-Bond
1	Ligan (co-crystal)	0,45 Å	-5.56 kcal/mol	83.98 µM	9

The validation results are demonstrated through good overlay visualization, as shown in Figure 1, indicating that the results are valid and ready to be used for molecular docking on the test compounds.

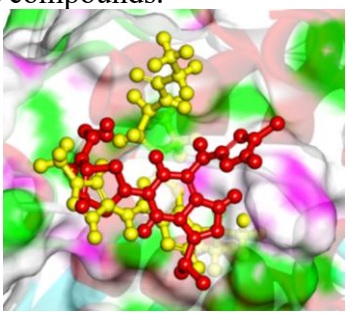


Figure 1. Comparison of conformations between the original ligand before validation (yellow) and the ligand after validation (red).

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Results of the Molecular Docking Process

Molecular docking simulations were performed using MGL Tools version 1.5.6 integrated with AutoDockTools 4.2. The Eaph1 receptor that had previously undergone preparation and validation procedures was subsequently employed as the target macromolecule for docking analyses involving the selected test compound ligands. The outcomes obtained from these docking studies are presented in Tables 4 and 5.

Table 4. Molecular Docking Results of Test Compounds

No	Compound Name	ΔG	KI	H-Bond
1	Sesamin	-6,21 kcal/mol	28,22 µM	7
2	Nobiletin	-5,51 kcal/mol	90,71 µM	5
3	Beta-Stigmasterol	-5,22 kcal/mol	148,5 5 µM	9
4	Linderflavone	-5,17 kcal/mol	161,4 3 µM	8
5	Ageconyflavone	-5,35 kcal/mol	119,6 4 µM	6

Source: Primary data, 2024

Table 5. Amino Acid Residues Contributing to the Receptor

No	Compound	Amino Acid Residues
1	Ligan (co-crystal)	ASP984, GLN976, ASP974, ARG977, VAL980, ILE981, LEU979, GLU985, ARG973, PRO975, TYR978, GLY983
2	Sesamin	GLN976, GLU985, ILE981, ASP984, ARG977, VAL980, LEU979, ASP974, PRO975, ARG973, THR940
3	Nobiletin	ARG977, ASP974, PRO975, ILE981, ASP984, VAL980, GLY983, GLN976, LEU979, GLU985, GLN982
4	Beta-stigmasterol	ILE981, GLY983, ARG977, VAL980, GLU985, ASP984, GLN976
5	Linderflavone	GLU985, ARG977, VAL980, ILE981, ASP984, GLN976, PRO975, LEU979, ASP974, GLY983, ARG973. TYR978
6	Ageconyflavone	ARG977, ILE981, ASP984, GLN976, VAL980, LEU979, ASP974, GLU985, PRO975, ARG973, TYR978
7	*5,6,7,3'-Tetramethoxy-4', 5'-methylenedioxyflavone*	ARG977, ILE981, ASP984,

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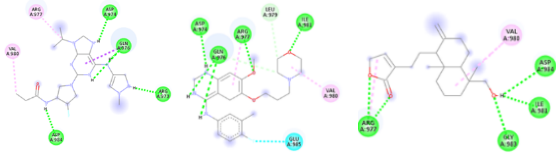
No	Compound	Amino Acid Residues
		VALL980, GLU985, ASP974, GLN976, PRO975, LEU979

Source: Primary data, 2024

Interaction Visualization Results

Amino acid residues interacting with the ligand were visualized using AutodockTools (ADT) and Discovery Studio (DS) software. The visualization of the control ligand and bandotan compound can be seen in Figure 2.



(a) (b) (c)

Figure 2. (a) Visualization result of the control co-crystal ligand; (b) Visualization result of the sesamin ligand; (c) Visualization result of theNobiletin compound.

DISCUSSION

Molecular docking was performed on *Ageratum conyzoides* phytochemical derivatives against the Human Cathepsin G–EapH1 receptor complex. Sesamin is one of the major bioactive constituents identified in *A. conyzoides* and has been reported to exhibit various biological activities, including antimicrobial effects demonstrated in several recent studies (Liaqat, 2021). These properties make sesamin a promising candidate for the development of plant-derived antimicrobial and anti-virulence agents.

The molecular docking analysis evaluated several parameters, including binding free energy (ΔG), inhibition constant (Ki), hydrogen bond interactions, and amino acid residues involved in ligand–receptor binding. These parameters are commonly used to assess the strength and stability of ligand–protein interactions and to predict the binding affinity of a compound toward its target receptor (Ihza Mahendra, 2021). In general, a greater number of favorable intermolecular interactions contributes to increased complex stability and may enhance the inhibitory potential of a ligand (Weni, Safithri, & Seno, 2020).

The docking results demonstrated that all tested compounds were capable of interacting with the active site of the Human Cathepsin G–EapH1 receptor, as indicated by their negative binding free energy values. Among the evaluated compounds, sesamin exhibited the lowest binding energy value (-6.21 kcal/mol), suggesting the strongest binding affinity toward the receptor. This finding is consistent with previous studies reporting that more negative binding affinity values indicate greater stability of the ligand–receptor complex and stronger intermolecular interactions (Weni et al., 2020; Rena et al., 2022). Sesamin also produced an inhibition constant (Ki) of 28.22 µM and interacted with seven amino acid residues within the binding pocket, further supporting its favorable binding characteristics.

The superior docking performance of sesamin compared with the other *A. conyzoides* derivatives may be attributed to its structural characteristics. Sesamin possesses a relatively rigid molecular framework consisting of two aromatic rings connected by methylenedioxy moieties. This rigid structure likely facilitates the formation of stable hydrophobic interactions within the receptor binding pocket while minimizing

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conformational entropy loss during binding. Furthermore, the oxygen atoms present in the ether groups can function as hydrogen bond acceptors, thereby contributing to additional stabilizing interactions with amino acid residues surrounding the active site. These structural features may collectively explain why sesamin generated the lowest binding energy among the tested compounds.

Compared with flavonoid derivatives such as nobiletin and ageconyflavone, sesamin contains fewer rotatable bonds, resulting in a more conformationally stable molecule during the docking process. Reduced molecular flexibility generally allows ligands to adopt energetically favorable orientations more efficiently within the active site. Consequently, sesamin may achieve a more optimal fit with key amino acid residues of the Human Cathepsin G–EapH1 receptor, leading to stronger binding affinity and lower docking energy values than the more flexible flavonoid compounds.

Analysis of amino acid interactions revealed that sesamin shared several binding residues with the native ligand, including ARG977, ASP974, PRO975, ILE981, ASP984, VAL980, GLY983, GLN976, LEU979, and GLU985. The presence of common interacting residues suggests that sesamin occupies the same binding pocket as the native ligand. This observation indicates that sesamin may inhibit the target protein through a mechanism similar to that of the native ligand while preserving the key intermolecular interactions may potentially serve protein inhibition. Such binding-site overlap is often considered an important indicator of competitive inhibitory potential.

From a pharmacophore perspective, sesamin possesses a favorable combination of hydrophobic features, aromatic ring systems, and hydrogen bond acceptor groups that can establish complementary interactions with the active site of the Human Cathepsin G–EapH1 complex. The aromatic rings contribute to hydrophobic and π-related interactions, whereas the oxygen-containing methylenedioxy groups provide hydrogen bond acceptor capabilities. The synergistic contribution of these pharmacophoric features likely plays a major role in the superior docking performance of sesamin and may explain its ability to achieve the most favorable binding affinity among the compounds evaluated in this study.

In addition to molecular docking results, all evaluated compounds satisfied Lipinski's Rule of Five, indicating favorable drug-likeness properties and potential suitability as orally administered drug candidates. The absence of violations related to molecular weight, lipophilicity (LogP), hydrogen bond donors, and hydrogen bond acceptors suggests that these compounds may possess adequate membrane permeability and oral bioavailability. Furthermore, all compounds exhibited intestinal absorption values exceeding 80%, indicating good potential for gastrointestinal absorption. The predicted skin permeability values also met the established criteria, suggesting sufficient membrane penetration capability. Toxicity prediction analysis revealed variations in toxicity classes among the compounds, which may provide useful information for prioritizing candidate molecules for further

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experimental validation and drug development studies.

CONCLUSION

This study demonstrated that all *Ageratum conyzoides* derivatives were capable of interacting with the Human Cathepsin G–EapH1 complex based on molecular docking analysis. Among all tested compounds, sesamin exhibited the most favorable binding affinity, as indicated by the lowest binding energy and inhibition constant values, and shared key amino acid residues with the native ligand within the binding pocket. In addition to satisfying the drug-likeness criteria defined by Lipinski's Rule of Five, ADMET prediction results also revealed promising pharmacokinetic properties. Nevertheless, these findings remain predictive in nature; therefore, further validation through molecular dynamics simulations, *in vitro* studies, and *in vivo* experiments is required to indicates the biological activity of sesamin as a potential Human Cathepsin G–EapH1 inhibitor.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' DECLARATION

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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