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Article

Molecular docking, prediction of drug-likeness properties, and toxicity risk assessment of compounds from Cinnamomum zeylanicum as inhibitors of Dengue DEN2 NS2B/NS3.

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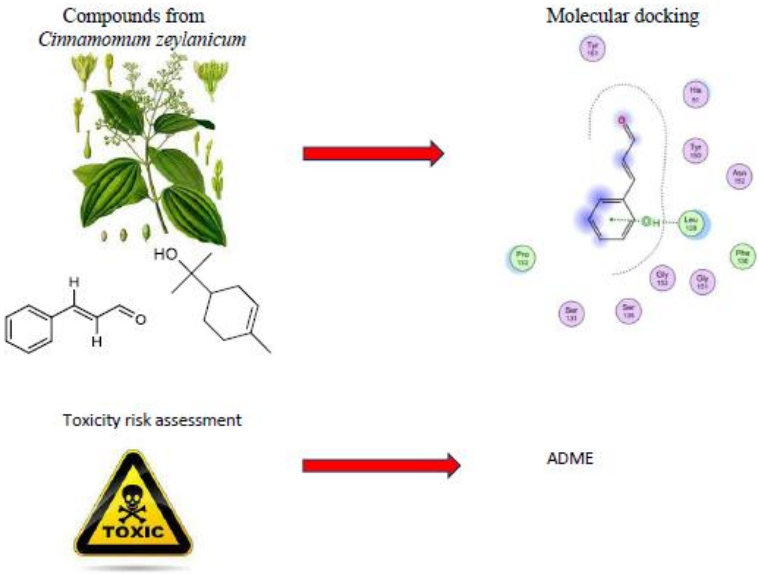
Abstract

Dengue hemorrhagic fever (DHF) is a serious mosquito-borne disease caused by the dengue virus, most often transmitted by the bite of female *Aedes aegypti mosquitoes*. In Indonesia, the number of DHF cases has steadily increased since the disease was first reported, underscoring the urgent need for effective treatments. This study used in silico methods to explore the potential of three bioactive compounds from *Cinnamomum zeylanicum* i.e. cinnamaldehyde, α-terpineol, and chavicol as inhibitors of the dengue virus NS2B/NS3 protease and evaluated their drug-likeness and potential toxicity. The compounds sourced from the NADI database were compared with panduratin A as a positive control. Molecular docking was performed using the Molecular Operating Environment (MOE) 2023.0901 software, and drug-likeness and toxicity predictions were performed using SwissADME and Protox-II. Among the tested compounds, α-terpineol exhibited the strongest potential to inhibit NS2B/NS3, while all three met the standard drug-likeness criteria. Notably, α-terpineol demonstrated the most favorable safety profile compared to cinnamaldehyde, chavicol, and panduratin A

Keywords: *Cinnamomum zeylanicum; Dengue DEN2 NS2B/NS3; Docking; Drug-likeness; Toxicity*

Graphical Abstract



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Introduction

Dengue hemorrhagic fever (DHF) is an infectious disease caused by a virus that is transmitted by a vector. Dengue infection is caused by the dengue virus. This virus belongs to the arbovirus group (arthropod-borne virus) within the genus Flavivirus and family Flaviviridae. The dengue virus has four serotypes: dengue virus 1, 2, 3, and 4 (DENV-1, DENV-2, DENV-3, and DENV-4). The most common serotype of dengue virus that causes infection in the human body is DENV-2. Replication of DENV-2 requires a complex of non-structural proteins, specifically protein non-structural 3 (NS3) and its cofactor (NS2B), known as NS2B/NS3 serine protease. NS3 is responsible for proteolytic processes of viral proteins, whereas NS2B acts as a cofactor for the replication of DENV-2. It is likely that this protease could be a potential target for dengue drugs by blocking the interaction between the NS3 protease and its cofactor protein NS2B [1].

Dengue fever remains a global health concern, with an alarming increase in the number of dengue cases reported each year. The DEN2 NS2B/NS3 protease is a pivotal target in the development of antiviral agents, making it a promising target for drug discovery [2]. Currently, no specific antiviral drug has been approved for this disease. In this study, compounds were obtained from a database, that is NADI database which is a natural product collection. The NADI database contained of 77 compounds found in *Cinnamomum zeylanicum,* commonly known as cinnamon. Among these 77 compounds, three were selected for the molecular docking studies: cinnamaldehyde, α-terpineol, and chavicol.

Cinnamaldehyde, the primary compound in cinnamon essential oils, exhibits diverse pharmacological activities, including antimicrobial, antioxidant, and immunomodulatory effects [3]. It has demonstrated efficacy against various bacterial and fungal pathogens in experimental models, making it a promising lead for the development of anti-infective drugs [3]. Phenolic compounds, including those found in cinnamon, have demonstrated antiviral activity against the dengue virus (DENV) through multiple mechanisms targeting viral particles, proteins, and host pathways [4]. Natural compounds and their analogs, such as alkaloids, phenols, and terpenoids, have shown potential in inhibiting DENV entry and replication [5]. Cinnamon and its constituents, particularly cinnamaldehyde, exert antibacterial effects by damaging cell membranes, inhibiting ATPases, cell division, and biofilm formation, and disrupting quorum sensing [6]. These findings support the exploration of cinnamon-derived compounds as potential therapeutic agents for various microbial infections. Thus, in this research three of these compounds (i.e cinnamaldehyde, α-terpineol, and chavicol) are investigated as potential ligands in molecular docking studies to assess their inhibitory activity against the Dengue virus serotype 2 (DEN2) NS2B/NS3 protease.

Recent studies have explored the potential of phytochemicals as inhibitors of dengue virus (DENV) NS2B/NS3 protease, a crucial target for antiviral drug development. In silico approaches, including molecular docking, ADMET analysis, and molecular dynamics simulations, have been employed to screen and evaluate natural compounds against this enzyme [7-9]. These investigations identified several promising phytochemicals with high binding affinities and favorable pharmacokinetic profiles. Notable compounds include erycristagallin, osajin, papraineA, and aloe-emodin [7], as well as 3',4'-methylenedioxy-7,8-(2",2"-dimethylpyrano)-flavone and limonianin [8]. Additionally, compounds CID-440015 and

CID-7424 have shown potential as novel anti-dengue agents [8]. These studies highlight the promise of natural products in the development of effective therapies against dengue fever, addressing the current lack of approved antiviral treatments for this globally significant disease.

Molecular docking is a computational technique that offers a unique perspective on the interactions between isolated compounds from *Cinnamomum zeylanicum* and DEN2 NS2B/NS3 protease [10]. Simultaneously, evaluating the drug-likeness properties of these compounds is a crucial step in identifying those that not only interact favorably with the target, but also possess the necessary characteristics for successful drug development [11]. Predicting drug-likeness streamlines the selection process by highlighting the candidates with optimal pharmacokinetic and also pharmaceutical attributes.

Materials and Methods

Molecular Docking

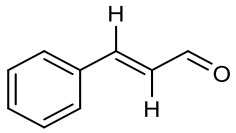
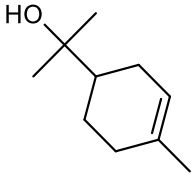
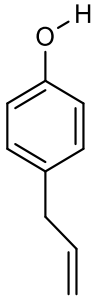
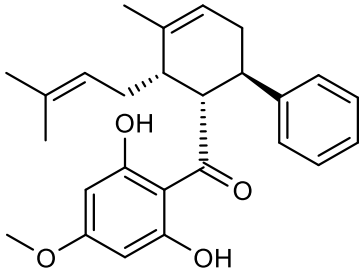
The molecular structures of the three compounds and panduratin A, which was used as a positive control, were sketched using ChemDraw 2015. Subsequently, the 3D structures of these ligands were energetically optimized using the MOE 2023.0901 software with the MMFF94x force field and a gradient of 0.0001. A ligand database in the *mdb format was generated by incorporating all the molecular structures. Table 1 lists the molecular structures of the positive controls and molecular structures of all the ligands. The three-dimensional crystal structure of the dengue virus NS2B/NS3 protease (PDB ID: 2FOM) was retrieved from the Protein Data Bank (www.rcsb.org). Pre-processing of the protein was carried out using Discovery Studio Visualizer (DSV, BIOVIA) by removing water molecules, bound ligands, and chloride ions. The structure was then energy-minimized in MOE using the CHARMM27 force field with an RMS gradient of 0.01 kcal/mol/Å. The binding site was identified using MOE's Site Finder module, with Site 13—comprising residues His51, Lys74, Asp75, Gly151, Asn152, Gly153, and Val154—selected as the docking target and defined as a dummy atom.

In MOE 2023.0901, docking simulations were performed using the London dG scoring function for initial posture generation and the Triangle Matcher placement approach. Force-field-based minimization was used for refinement, and the GBVI/WSA dG scoring algorithm was used for final rescoring. The best 10 poses with the lowest binding free energy (ΔG, kcal/mol) were selected for additional examination from 50 poses created for each ligand. The MOE Ligand Interaction Analysis tool was used to analyze and visualize protein–ligand interactions, such as hydrogen bonds, hydrophobic contacts, and van der Waals interactions, using DSV.

ADMET Profiling and Toxicity Prediction

To acquire ADME profiling and toxicity predictions, the process involved retrieving the SMILES formula for the chemical structures of compounds cinnamaldehyde, α-terpineol, and chavicol. These structures were obtained from the PubChem website by visiting the following link: https://pubchem.ncbi.nlm.nih.gov/. SwissADME (accessible at http://www.swissadme.ch/index.php) was used for further analyses. Additionally, in silico toxicity data were obtained through the Protox II website by navigating to the following link: https://tox-new.charite.de/. Facetox predictions were performed.

Table 1: Molecular structure of ligands and positive control

No	Molecular name	Molecular structure
Compound 1	***Cinnamaldehyde*** *(E)-3-phenylprop-2-enal* Molecular formula: C_9H_8O Molecular weight: 132.16 g/mol	
compound 2	***α -Terpineol*** *2-(4-methylcyclohex-3-en-1-yl) propan-2-ol* Molecular formula: $C_{10}H_{18}O$ Molecular weight: 154.25 g/mol	
compound 3	***Chavicol*** *4-allylphenol* Molecular formula: $C_9H_{10}O$ Molecular weight: 134.17 g/mol	
Positive control	**Panduratin A** *(2,6-dihydroxy-4-methoxyphenyl) ((1R,2R,3S)-4-methyl-3-(3-methylbut-2-en-1-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl) methanone* Molecular formula: $C_{26}H_{30}O_4$ Molecular weight : 406.5 g/mol	

Result and Discussion

Molecular Docking

The molecular docking results for three of these compounds are presented in Table 2. Figure 1 shows the spatial arrangement of panduratin A as a positive control. Based on the docking results, Panduratin A used as a positive control, exhibited a binding free energy of -6.55 kcal/mol with an RMSD value of 1.65 Å. It can interact with 10 amino acid residues at the active site of the receptor. These residues included His51, Arg54, Asp75, Tyr161, Val72, Gly151, Leu128, Asn152, Gly153, and Ser135. The visualization of the docking results indicated that Panduratin A formed a hydrogen bond interaction with the phenyl group of His51, where the phenyl group serves as the hydrogen bond acceptor, as denoted by the green dashed lines. Additionally, Panduratin A engage in hydrophobic interactions with Arg54, represented by a blue ring, and with Asp75 through Van Der Waals interactions, marked by a red ring. Spatial arrangement of panduratin A is presented in Figure 1.

In the docking results of compound **1** (Table 2), it was observed that the binding free energy is -4.51 kcal/mol, with an RMSD value of 1.01 Å. Compound **1** binds to 11 amino acid residues at the active site of the receptor. These residues included Leu128, Tyr161, His51, Tyr150, Asn152, Phe130, Gly151, Gly153, Ser135, Ser131, and Pro132. Visualization of the docking results for compound 1 revealed interactions with various amino acid residues, including hydrogen bond interactions with Leu128's phenyl group, where the phenyl group acts as a hydrogen bond acceptor, marked by

green dashed lines. Additional interactions were observed between Tyr161, His51, Tyr150, Asn152, Phe130, Gly151, Gly153, Ser135, Ser131, and Pro132. It is worth noting that compound **1** shares only five amino acid residues in common with the positive control (binding factor) in the docking results, specifically in interactions with Tyr161, Asn152, Gly151, Gly153, and Ser135. Spatial arrangement of compound **1** is presented in Figure 1.

Table 2. Docking results

Compound	Binding free energy (kcal/mol)	RMSD	H bond	Hydrophobic interaction	van der Waals	The others interaction	Binding Factor
Positive control Panduratin A	**-6.5575**	**1.6514**	**His 51**	**Arg54**	**Asp75**	**Tyr 161, Val 72, Gly 151, Leu 128, Asn 152, Gly 153, Ser 135**	**10**
compound 1	-4.5104	1.0129	Leu 128	-	-	**Tyr 161,** His 51, Tyr 150, **Asn 152,** Phe 130, **Gly 151, Gly 153, Ser 135,** Ser 131, Pro 132	5
Compound 2	-4.9748	1.1528	**His 51**	-	-	**Tyr 161, Gly 153, Asn 152, Leu 128,** Tyr 150, Phe 130, **Ser 135,** Ser 131, **Gly 151,** Pro 132	7
Compound 3	-4.7247	1.0358	Leu 128, Phe 130	-	-	**Tyr 161,** His 51, Tyr 150, **Asn 152, Gly 151, Gly 153, Ser 135,** Ser 131, Pro 132	5

Note: compound 1 is cynamaldehyde; compound 2 is *α -Terpineol*; compound 3 is chavicol

Compound **2** was obtained the binding free energy of -4.97 kcal/mol and an RMSD of 1.15 Å. Compound **2** can bind to 11 amino acid residues in the active site of the receptor, including His51, Tyr161, Gly153, Asn152, Leu128, Tyr150, Phe130, Ser135, Ser131, Gly151, and Pro132. Visualization of the docking results for compound 2 revealed interactions with the catalytic triad amino acid residue His51 through hydrogen bonding on the benzene group, where the benzene group acts as a hydrogen bond donor, indicated by green dashed lines. It also interacts with other bonds in the amino acid residues Tyr161, Gly153, Asn152, Leu128, Tyr150, Phe130, Ser135, Ser131, Gly151, and Pro132.The docking results for compound **2** share seven amino acid residues in common with the positive control (binding factor), which were found in

amino acid residues His51 through hydrogen bonding and other interactions with amino acid residues Tyr161, Gly153, Asn152, Leu128, Ser135, and Gly151. Figure 1 is presented the spatial arrangement of compound **2** with protein.

Compound **3** showed a binding free energy of -4.72 kcal/mol and an RMSD of 1.03 Å. Compound **3** can bind to 11 amino acid residues in the active site of the receptor, including Leu128, Phe130, Tyr161, His51, Tyr150, Asn152, Gly151, Gly153, Ser135, Ser131, and Pro132. Visualization of the docking results for compound 3 (Figure 1) revealed the amino acid residues involved in hydrogen bonding interactions. Specifically, Leu128 forms a hydrogen bond with the phenol group, which acts as a hydrogen bond acceptor, as indicated by the green dashed lines. Additionally, the amino acid residue Phe130 is involved in a hydrogen bond interaction with the hydroxyl group, where the hydroxyl group acts as a hydrogen bond donor, indicated by blue dashed lines with an arrow pointing towards amino acid residue Phe130. Compound 3 also interacted with other bonds in the amino acid residues Tyr161, His51, Tyr150, Asn152, Gly151, Gly153, Ser135, Ser131, and Pro132. The docking results for compound **3** share only five amino acid residues with the positive control (binding factor), which are involved in other interactions, including amino acid residues Tyr161, Asn152, Gly151, Gly153, and Ser135.

The activity of the tested compounds against dengue NS2B/NS3 protease, as shown in Table 1 and Figure 1, can be attributed to a combination of molecular interaction parameters and inherent chemical structure features. Binding free energy is a primary determinant, with more negative values indicating a stronger binding affinity. Among the tested compounds, α-terpineol exhibited the most favorable binding free energy (−4.97 kcal/mol), compared to cinnamaldehyde and chavicol, suggesting enhanced stability of the ligand–protein complex.

Hydrogen bonding patterns play a critical role in stabilizing the ligand orientation within the active site. α-Terpineol formed hydrogen bonds with the catalytic residue His51, a key interaction also observed with the positive control, contributing to its superior binding performance. In contrast, cinnamaldehyde and chavicol, although forming hydrogen bonds (e.g., with Leu128 or Phe130), lacked interactions with His51, which may explain their relatively lower binding affinities.

The structural differences among the compounds also influenced their activity. α-Terpineol's cyclic terpene backbone and hydroxyl group enable both hydrophobic contacts with non-polar residues (e.g., Tyr161, Leu128) and polar interactions through hydrogen bonding. Cinnamaldehyde, with its conjugated aldehyde group, offers planarity and π–π stacking potential; however, the absence of strong polar anchoring in the catalytic triad may limit its binding strength. Chavicol, which features an allylphenol structure, allows hydrogen bonding through its hydroxyl group but exhibits weaker hydrophobic complementarity than α-terpineol.

The docking results obtained in this study are consistent with previously reported findings for cinnamon-derived compounds. Cinnamaldehyde has been shown to exert antiviral effects against influenza A and herpes simplex viruses in vitro, with proposed mechanisms involving the inhibition of viral envelope fusion and suppression of replication [12]. In vivo

studies have further demonstrated its anti-inflammatory and immunomodulatory effects, which could indirectly contribute to its antiviral efficacy [13]. Similarly, α-terpineol possesses antimicrobial and antifungal properties and, in some cases, has displayed inhibitory effects against enveloped viruses, such as herpes simplex virus type 1 [14]. Although fewer antiviral studies are available for chavicol, phenolic derivatives with similar allyl side chains have demonstrated antibacterial, antifungal, and moderate antiviral activities

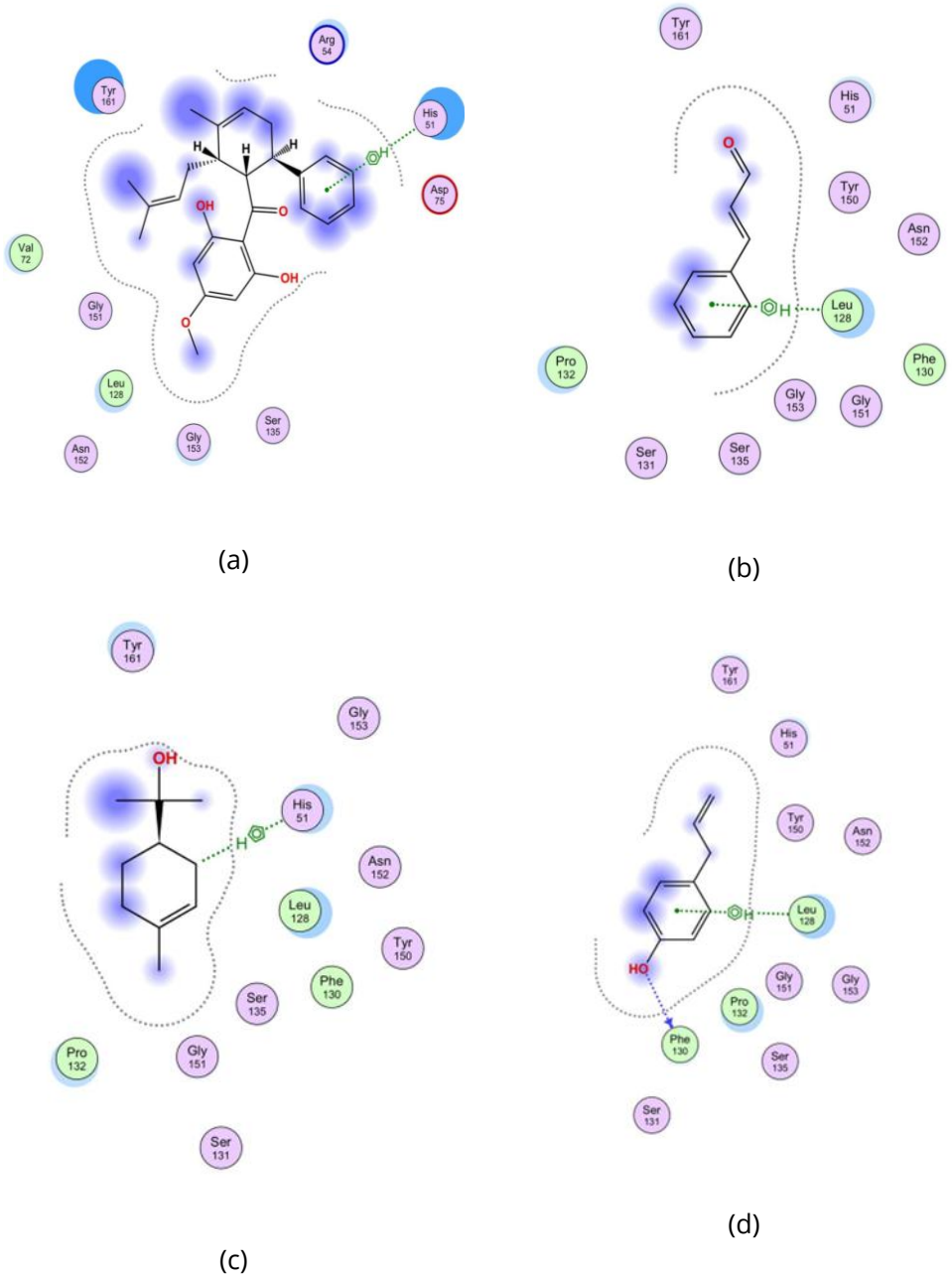
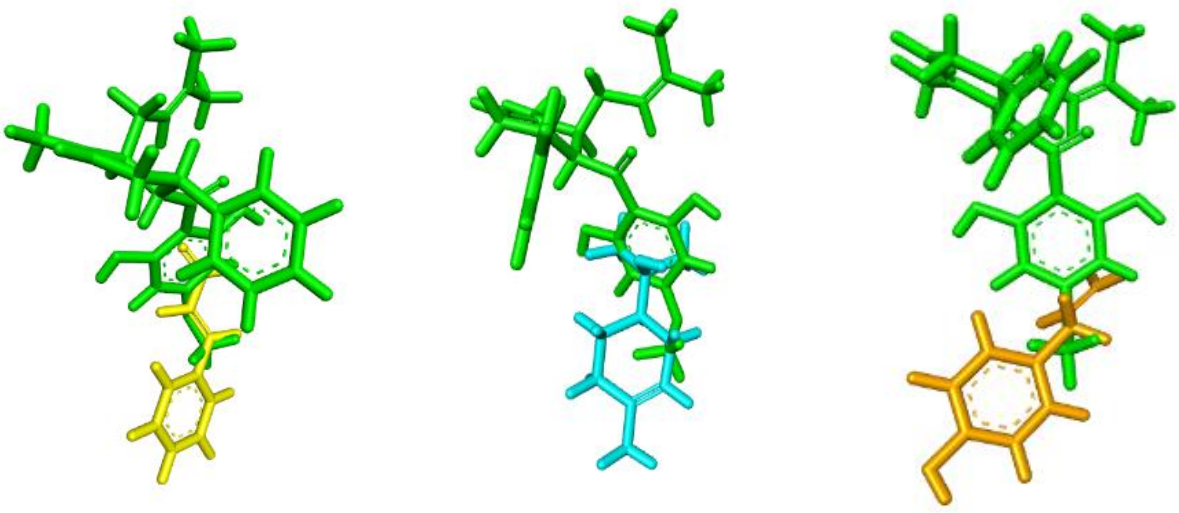


Figure 1: Spatial arrangement of (a) panduratin A (b) compound **1** (c) compound **2** (d) compound **3**

When comparing docking affinities, the binding free energies of α-terpineol and cinnamaldehyde against dengue NS2B/NS3 in our study are in line with previous computational investigations on terpenoid and phenylpropanoid derivatives, which reported similar interaction patterns with catalytic residues such as His51 and Asp75 [15]. These findings suggest that the antiviral potential of cinnamon-derived compounds observed in vitro and in vivo may be partially explained by their ability to interact with key active site residues of viral proteases, as indicated by our in silico results.

Superimposition depicted the conformational pose of the compound structure that best aligns with the positive control [16]. Based on the superimposition results (Figure 2) of compounds 1 (cinnamaldehyde), 2 (α-terpineol), and 3 (chavicol) with the positive control (panduratin A), compound 2 (α-terpineol) was found to bind more effectively to the active site, forming a complex and sharing similar interactions with the positive control. Based on these findings, compound 2 (α-terpineol) could be categorized as a potential inhibitor of dengue NS2B/NS3



(a) (b) (c)

Figure 2. Superimposisition of panduratin A (green) with (a) compound 1 (b) compound 2 and (c) compound 3

ADMET profiling and toxicity prediction

The findings from the SwissADME analysis for the three compounds isolated from *Cinnamomum zeylanicum*, specifically cinnamaldehyde, α-terpineol, and chavicol along with the panduratin A as positive control, have yielded drug-likeness parameters, as detailed in Table 3.

The molecular weights obtained for compounds **1** (132.16 g/mol), **2** (154.25 g/mol), **3** (134.18 g/mol), and panduratin A (406.51 g/mol) respectively, fall within the acceptable range as they have molecular weights below the Lipinski rule's threshold of <500 g/mol [17]. Molecular weight is known to influence the ability of a compound to passively diffuse through cell membranes. If a compound has a molecular weight (MW) of >500 g/mol, its ability to diffuse through cell membranes becomes more challenging [18]. Molecular weight also affects intestinal absorption, blood-brain barrier penetration, elimination rate, and interactions with target receptors [19].

Table 3. Drug-likeness

Compound	*MW (g/mol)*	*Log P*	*Hydrogen Bond Donor (HBD)*	*Hydrogen Bond Acceptor (HBA)*	*Topological Polar Surface Area (TSPA Å)*	*Rotable Bond*	*Drug-Likeness*
Cinnamaldehyde	132.16	1.97	0	1	17.07	2	Yes Score: 0.55
α-Terpineol	154.25	2.58	1	1	20.23	1	Yes Score: 0.55
Chavicol	134.18	2.33	1	1	20.23	2	Yes Score: 0.55
Panduratin A	406.51	4.77	2	4	66.76	6	Yes Score: 0.55
Parameter	< 500[9]	< 5[9]	< 5[9]	< 10[9]	≤ 140[10]	< 10[10]	-

Based on the obtained Log P values for compounds 1 (1.97), 2 (2.58), 3 (2.33), and panduratin A (4.77), they met the Lipinski rule criterion with Log P values below of five [20]. Log P is a parameter that describes a compound's ability to dissolve in octanol/water (biological membrane). As the Log P value increases, the compound becomes more hydrophobic. Compounds that are excessively hydrophobic tend to have higher toxicity because they remain trapped in lipid bilayers and are distributed extensively within the body, reducing target-binding selectivity. Conversely, if a compound's Log P value is more negative, crossing the lipid bilayers may be difficult [20].

The Compounds **1, 2, 3,** and panduratin A had hydrogen bond donor values of 0, 1, 1, and 2, respectively, while their hydrogen bond acceptor values were 1, 1, 1, and 4. It can be said that the hydrogen bond donor and acceptor values are good as they meet the Lipinski rule of having hydrogen bond donor values less than 5 and hydrogen bond acceptor values is less than 10 [17]. hydrogen-bond donor and acceptor values are parameters used to describe the hydrogen-bond capacity of a compound required in the absorption process. If the number of hydrogen bond donors is >5 and the number of acceptors >10, the energy required for the absorption process is higher. The higher the number of hydrogen bond donors and acceptors, the higher the energy required for absorption process to occur [20].

The Topological Polar Surface Area (TPSA) has a value of ≤140 Å and the number of rotatable bonds (rotable bonds) has a value of <10 [21]. TPSA is defined as the sum of the surface areas of polar atoms (mainly oxygen or nitrogen, including bound hydrogen) in a molecule. This parameter has been successfully applied to predict human intestinal absorption, single-layer CaCo-2 cell permeability, and blood-brain barrier penetration [22]. Based on the results obtained, the TPSA values of compounds 1, 2, 3, and A indicated good absorption with TPSA values ≤140 Å.

The numbers of rotatable bonds for compounds **1, 2, 3,** and pandurtatin A were 2, 1, 2, and 6, respectively, which were all within the acceptable range. Lipinski's rule of five limits the number of rotatable bonds to no more than ten (rotatable bonds <10) for

drug candidates [21]. Rotatable bonds are defined as the number of single bonds, excluding bonds in rings that can rotate freely around themselves.

Table 4: Prediction toxicity level

Compound	LD_{50}	Toxicity Level[11]	Hepatotoxicity
Cinnamaldehyde	1850 mg/kg	Class IV	Inactive
α-Terpineol	2830 mg/kg	Class V	Inactive
Chavicol	870 mg/kg	Class IV	Inactive
Panduratin A	2000 mg/kg	Class V	Inactive

Generally, toxicity of compounds could be classified into six classes. Class 1 with $LD_{50} \leq 5$, class II consist of compounds with LD_{50} value ranging from 5 to 50, class III consist of compounds with LD_{50} value ranging from 50 to 300. Compounds falling into class IV have LD_{50} values from 300 to 2000. Class V comprises compounds with LD_{50} between 2000 to 5000. Finally, class VI includes compounds with $LD_{50} > 5000$ [23]. Compounds **1, 2, 3** and the positive control (panduratin A) have LD_{50} values of 1850 mg/kg, 2830, 870, and 2000 mg/kg, respectively. In this context, LD_{50} values within the range of $300 < LD_{50} \leq 5000$ mg/kg indicate relatively low toxicity, falling into toxicity classes IV and V, which are considered safe [23]. Toxicity prediction suggests that the smaller the numerical value, the more toxic the compound is predicted to be; conversely, the larger the numerical value, the safer the compound [24].

The results of the Protox-l I analysis are displayed in Table 4, illustrating the toxicity levels observed in rodents for the three isolated compounds from *Cinnamomum zeylanicum*, cinnamaldehyde, α-terpineol, and chavicol along with the panduratin A as positive control. Hepatotoxicity indicated the level of damage caused by compounds in the liver. Compounds that can significantly induce hepatotoxicity may lead to liver damage, and are a major reason why drugs may not be marketed [25]. In the drug discovery process, drug-induced liver injury (DILI) is the most serious concern, as it often leads to the termination of drug development programs [26]. Based on the prediction results in this study, as presented in Table 4, it was found that none of the tested compounds exhibited hepatotoxicity, and they were considered inactive. Therefore, it can be concluded that panduratin A, compound **1**, compound **2**, and compound **3** are safe to use and do not cause harm to the live.

Conclusion

Docking of three isolates from cinnamon (*Cinnamomum zeylanicum*) predicted that compound 2 (α-terpineol) has the potential to inhibit dengue NS2B/NS3. Compound **2** (α-terpineol) has binding free energy more negative than compounds **1** (cinnamaldehyde) and **3** (chavicol). However, it was not more negative than Panduratin as the positive control. Based on the drug-likeness property predictions, all test compounds exhibited good drug-likeness parameters according to Lipinski and Veber's rules. In terms of safety, compound

2 (α-terpineol) was safer than compounds 1 (cinnamaldehyde), 3 (chavicol), and panduratin A, as it had an LD_{50} value of 2830 mg/kg, classifying it as practically non-toxic (toxicity class V). Thus, compound **2** (α-terpineol) has potency become new inhibitor for dengue DEN2 NS2B/NS3.

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Author Contributions

All authors have read and agreed to the published version of the manuscript. Conceptualization, research design, and methodology: N.F, A. F, Validation: N.F, A.F, B.I. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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