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A New Insight Into Toxicity of Database Compounds from Ginger *(Zingiber officinale)* by Modelling Study

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Abstract

Dengue haemorrhagic fever (DHF) is an infectious disease caused by the dengue virus. The dengue virus is transmitted through female mosquitoes, especially *Aedes aegypti* and *Aedes albopictus*. Indonesia is a dengue endemic country, and almost all provinces in Indonesia are infected with dengue. However, targeted antiviral drugs against dengue virus (DENV) are not yet available. This study aimed to determine the potential of three compounds isolated from ginger (*Zingiber officinale*) as dengue NS2B/NS3 inhibitors, and to predict the physicochemical properties (drug-likeness) and potential toxicity of drug candidates. Ginger isolates in the form of [8]-gingerol, [6]-paradol, shogaol were obtained from the Natural Discovery Database (NADI). Toxicity and drug-likeness predictions were performed using ProTox-II and SwissADME, and Molecular Operating Environment (MOE) 2022.0901 was used for the molecular docking process. Results: The results showed that the ginger compound (*Zingiber officinale*), [8]-Gingerol, [6]-Paradol, and Shogaol, had binding free energy of -7.18, -7.10 and -6.88 kcal/mol, respectively. It is indicated that three compounds had potentiality to inhibit the NS2B/NS3 protein complex with a binding free energy that was almost equivalent to that of the positive control, panduratin A, and similar to that of the positive control, which can be seen in superimposition. In addition, three compounds isolated from ginger met the drug-likeness parameters. Based on the analysis of in silico toxicity studies, the three compounds isolated from ginger showed different levels of toxicity. Therefore, based on the safety level of oral use, the [8]-gingerol compound is safer to develop as a dengue antiviral drug, where the LD_{50} value of [8]-gingerol is 2.580 mg/kg with a class V toxicity level that is practically nontoxic.

Keywords: *Zingiber officinale; dengue NS2B/NS; docking; toxicity;binding free energy*

Introduction

Dengue hemorrhagic fever (DHF) is an infectious disease caused by the dengue virus (DENV) in tropical and subtropical climates, and is transmitted through female mosquitoes, mainly *Aedes aegypti* and *Aedes albopictus* [1]. This illness is an infectious disease, for which the World Health Organization (WHO) has paid extra attention. According to Bhatt et al. (2013)[2], 390 million dengue virus infections have been documented worldwide.

Dengue virus belongs to a group of arthropod-borne viruses belonging to the genus Flavivirus and family Flaviviridae. This virus has four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) based on its genetic material. This

serotype difference causes infection with one serotype to prevent the formation of strong antibodies against dengue virus infection with other serotypes[3]. Several reports have stated that DENV-2 and DENV-3 cause more severe clinical manifestations than the other serotypes[4-6]. DENV-2 is the serotype that causes most infections in Southeast Asian countries[7].

There are five known dengue virus serotypes: DENV-1, DENV-2, DENV-3, DENV-4, and DENV-5. The most severe strain of the dengue virus, DENV-2, circulates in Southeast Asian nations with a very high incidence[8]. DENV-2 infection is significantly associated with severe dengue. The maturation of viral polyproteins is dependent on the non-structural serine protease 3 (NS3). The protease complex NS2B-NS3 is formed when serine protease NS3 binds to cofactor NS2B[9]. This complex is necessary for cleavage of the viral precursor polyprotein, which is essential for DENV-2 replication. Consequently, interference of an inhibitor with the activity of the NS2B-NS3 protease complex can prevent viral replication. Therefore, the development of dengue antivirals could be employed as a prospective target[10].

Natural products from plant extracts are a potential source for many types of modern medicine. Ginger (*Zingiber officinale*) has been confirmed to have antiviral activity. Many bioactive compounds, including phenolic compounds and terpenes, have been identified in the ginger. Phenolic compounds, especially gingerols, shogaols and paradols, explain the various bioactivities of ginger [11]. In recent years, ginger has been found to have biological activities, such as antioxidant[12], anti-inflammatory[13], antimicrobial [14], and anticancer[15].

Several studies have shown that ginger is a potential antiviral agent. Based on research conducted by Kaushik et al. (2020)[16] found that the aqueous extract of ginger exhibited inhibitory activity against chikungunya virus. Chang et al. (2013)[17] reported that ginger can inhibit plaque formation induced by human respiratory syncytial virus in respiratory mucosal cells by secreting interferon-β, which neutralizes viral infections. Meanwhile, a study by Wang et al. (2020) [18] also reported that the compound Gingerenone A found in ginger suppresses the replication of three subtypes of influenza A virus (IAV) (H1N1, H5N1, and H9N2).

The compounds used in this study were obtained from the NADI database, which is a collection of natural products. Three molecules derived from Zingiber officinale were selected for computer analysis. They were docked to assess the bioactivity. In silico prediction of physicochemical properties and toxicity was also performed to predict the physicochemical properties, pharmacokinetics, and potential toxicity of drug candidates. Therefore, the main goal of this study was to investigate potentiality of NS2B/NS3 serine protease inhibitors from *Zingiber officinale* against dengue virus.

Experimental

Materials and Methods

Molecular Docking

Three of compounds were obtained from a database, they are [8]-Gingerol, [6]-Paradol, and Shogaol. The database used in this research is http://nadi-discovery.com/ provides access to the structure of the molecule isolated from ginger (*Zingiber officinale*). Then, using the Chemdraw 15.0 program, the molecular structures of the ginger compound (*Zingiber officinale*), [8]-Gingerol, [6]-Paradol, and Shogaol, as well as the positive control (panduratin A), were drawn. Utilizing MOE 2022.0901 (Chemical Computing Group) with a force field of MMFF94x and a gradient of 0.0001, a three-dimensional (3D) structure of each ligand was created. Subsequently, a database of ligands in the *mdb format was created, and all structures were recorded. Table I lists the molecular structures of the ligands.

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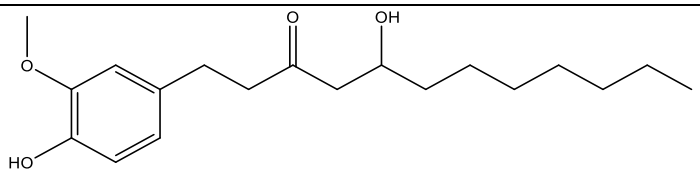
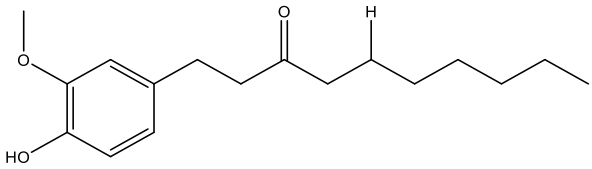
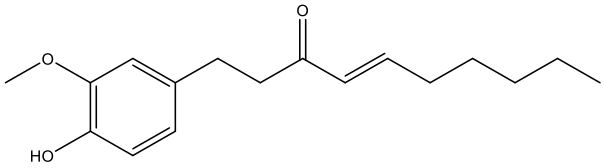
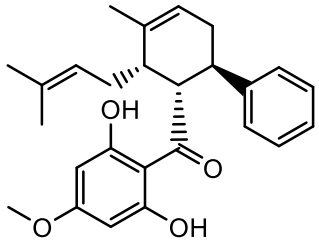
Table 1. Molecular structure of ligands

compound	Structure
[8]-gingerol	
[6]-paradol	
Shogaol	
Panduratin-A	

Using PDB ID 2FOM, the crystal structure of the dengue virus NS2B/NS3 serine protease was obtained from rcsb. org. The protein is composed of two chains, labeled as chain A and chain B. The removal of water molecules, initial (innate) ligands, and Cl^- ions from the protein was accomplished using DSV application. Using the MOE 2022.0901 software package's CHARMM27 force field and an RMS gradient of 0.01 kcal/mol/A, the energy of this protein's H atoms, alpha carbon atoms, and backbone atoms was minimized [19].

Site finder was used to identify the active site of the protein. Leu128, Asp129, Phe130, Ser131, Pro132, Ser135, Tyr150, Gly151, and Gly153 were among the amino acid residues that constituted Site 3, while His51, Lys74, Asp75, Gly151, Asn152, Gly153, and Val154 were among the amino acid residues that constituted Site 13, which served as the target site for the

docking process. The site was then set to a dummy atom on the dock menu, and the MDB file with the ready-made ligand structure was chosen as the ligand. Subsequently, the refinement was set to be rigid, the posture was set to 50 and 10, and the placement was set as a triangle. Additionally, a docking process was possible.

ADME Profiling and Toxicity Prediction

To obtain ADME profiling and toxicity prediction, the steps taken are to look for the SMILES formula for the chemical structure of compounds [8]-Gingerol, [6]-Paradol and Shogaol obtained from the PubChem website by opening the link site (https://pubchem.ncbi). nlm.nih.gov/). After obtaining the SMILES formula, SwissADME (http://www.swissadme.ch/index.php) was used. In silico toxicity information was obtained from the Protox II website by opening a site link (https://tox-new.charite.de/) followed by Facetox prediction.

Results and Disscusion

Molecular Docking

The molecular docking results for the three compounds are shown 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, had a bond free energy value of -7.02 with an RMSD value of 1.54 and could bind to 14 amino acid residues on the active site of the receptor, namely the amino acids His51, Pro132, Asp75, Tyr16, Ile36, Gly151, Ser135, Tyr150, Ser131, Phe130, Asn152, Leu128, Gly153, and Val52. The docking visualization results showed that panduratin A could bind to His51 and Pro132 amino acid residues via hydrogen bonding. The His51 amino acid has a hydrogen bond in the phenyl group; in this case, the phenyl group acts as a hydrogen bond donor, which is marked by the green dotted line. Panduratin A interacts with Asp75 amino acid residues through van der Waals interactions, which are marked with red rings[7,19]. Important amino acid residues in the catalytic triad located on the active site of NS2B/NS3 serine protease include His51, Ser135, and Asp75. The ability of a molecule to bind these three amino acid residues may help decrease the catalytic activity of NS2B and NS3. Because these three amino acid residues are involved in the breakdown of polyproteins necessary for viral replication, interaction with one of the three amino acid residues in the catalytic triad is crucial.

The docking approach was considered valid because the results for panduratin A had an RMSD of 2[20]. Lower RMSD results suggest docking mistakes or smaller deviation values.

Based on the docking results on [8]-gingerol, the binding free energy value was -7.18 kcal/mol and the RMSD value was 1.26. A comparison of the binding free energy values of panduratin A showed that the binding free energy of [8]-gingerol was more negative than that of panduratin A, indicating that [8]-gingerol could easily bind to the active site of NS2B/NS3 serine protease (2FOM). This is in accordance with the theory, which states that the more negative the free energy of a molecule, the more stable the molecule, and the reaction proceeds spontaneously.

[8]-Gingerol contained the same 10 amino acid residues as the positive control. This compound also interacts with the catalytic triad amino acid residue His51 via the formation of hydrogen bonds attached to the carbon chain. In addition, [8]-gingerol can also bind to the active site of 2FOM through van der Waals interactions, namely, the amino acid residue Asp75, which is marked with a red ring. Compound [8]-gingerol also has a hydrophobic bond with the amino acid residue Arg54, which is marked with a blue ring. This presumably causes these compounds to be more active than other compounds. The spatial arrangement of [8]-gingerol is depicted in Figure 2, and Figure 3 shows the superimposition of [8]-gingerol with panduratin A.

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Table 2. Docking results

Compound	Binding free energy (kcal/mol)	RMSD	Hydrogen bond	Van der Waals	Another interaction	Factor of binding
Panduratin A	-7.03	1.54	His51 Pro132	Asp75	Tyr161, Ile36 Gly151, Ser135 Tyr150, Ser131 Phe130, Asn152 Leu128, Gly153 Val52	14
[8]-gingerol	-7.18	1.26	**His51**	**Asp75**	Lys73, Val72 Val155, **Tyr161 Gly153,** Val154 Trp50, **Ser131 Leu128, Tyr 150** Pro132, **Phe130 Gly151, Ser135**	10
[6]-paradol	-7.10	1.32	**His51**	**Asp75**	Val72,**Tyr 161 Phe130,** Pro132 **Ser131, Gly151 Ser135, Leu128 Tyr150, Asn152 Gly153,** Trp50	11
Shogaol	-6.88	1.59	Tyr161, **His51**	**Asp75**	Val72, **Leu128** Trp50, Pro132 **Ser131, Tyr150 Phe130, Ser135 Gly 153, Gly151**	9

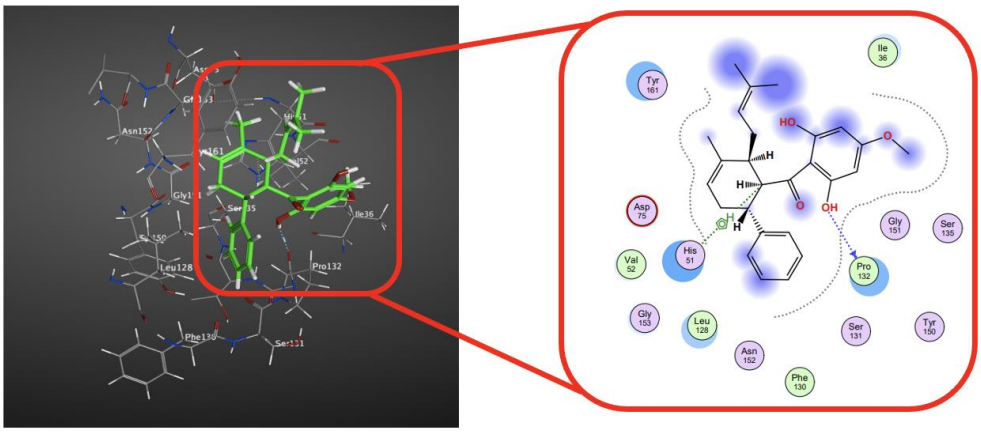

Figure 1. Spatial arrangement of Panduratin A as positive control

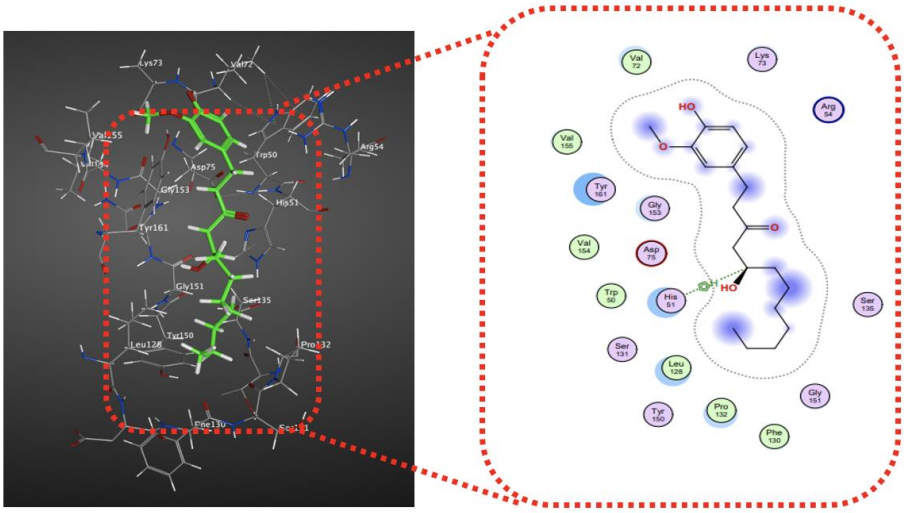

Figure 2. spatial arrangement of compound [8]-Gingerol

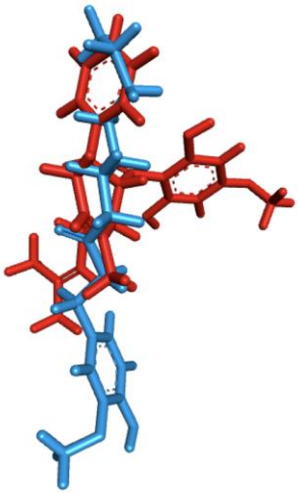

Figure 3. Superimposition of panduratin A (red) and compound [8]-gingerol

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The docking results of the [6]-paradol compound showed a binding free energy of -7.10 kcal/mol. The bond strength through bond free energy was close to that of the positive control, panduratin A. The results of this study were confirmed and validated based on an RMSD value of 1.32, it is less than <2 Å. [6]-paradol bond with 2FOM protein is stronger because its binding free energy is lower compared than positive control Panduratin A.

The docking results of the [6]-paradol compound showed a binding free energy of -7.10 kcal/mol. The bond strength based on the bond free energy was close to that of the positive control, panduratin A. The results of this study were confirmed and validated based on an RMSD value of 1.32, which was less than 2 Å. [6]-paradol bond with 2FOM protein is stronger because its binding free energy is lower compared than positive control Panduratin A.

The bonds produced by [6]-paradol are in the form of hydrogen interactions (with the bond site on amino acid His51), hydrophobic interactions (with the bond site on amino acid Arg54), van der Waals interactions (Asp75), and other interactions (with the bond sites on amino acids Val72, Tyr161, Phe130, Pro132, Ser131, Gly151, Ser135, Leu128, Tyr150, Asn152, Gly153, and Trp50). In addition, [6]-paradol also had the largest binding factor compared to the other compounds. The spatial arrangement of compound [6] is depicted in Figure 4.

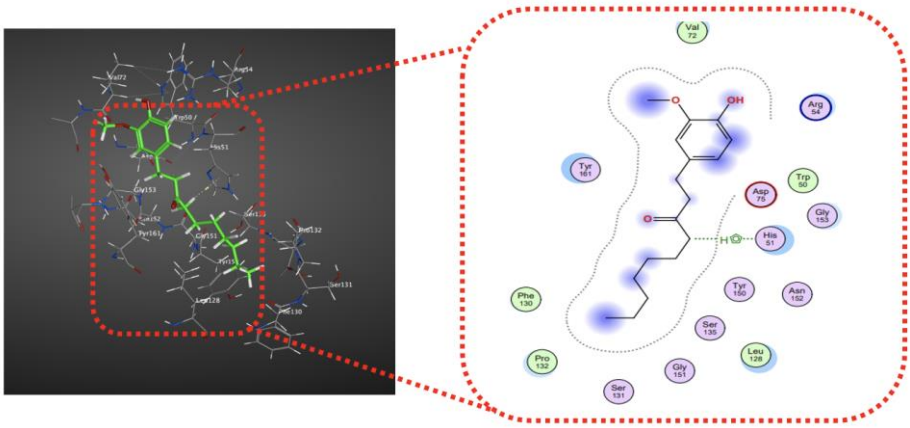

Figure 4. spatial arrangement of compound [6]-Paradol

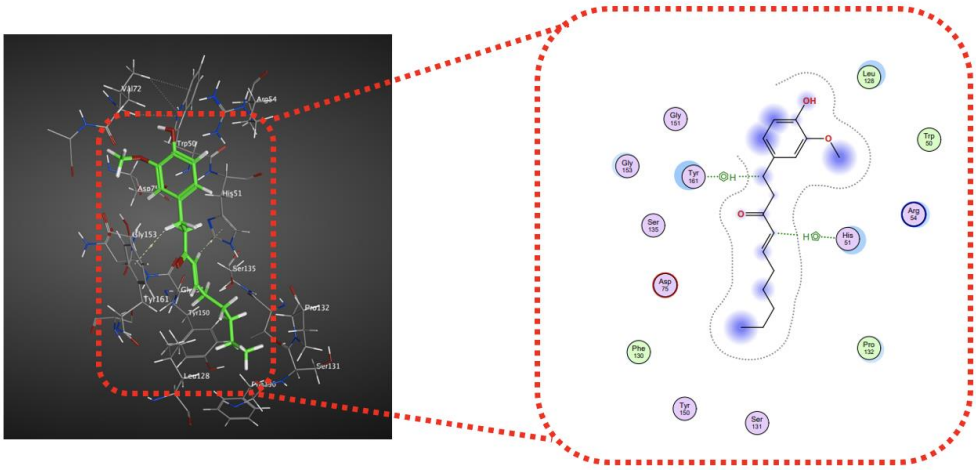

Figure 5. spatial arrangement of compound Shogaol

The docking results showed that shogaol has a binding free energy of -6.88 kcal/mol with an RMSD value of 1.59. Based on the active bond site, shogaol interacts with various amino acid residues to form hydrogen bonds (Tyr161 and His51), hydrophobic bonds (Arg54), Van Der Waals bonds (Asp75), and other bonds (Val72, Leu128, Trp50, Pro132, Ser131, Tyr150, Phe130, Ser135, Gly153, and Gly151). Spatial arrangement of shogaol is presented in Figure 5.

ADME *Profiling* and Toxicity Prediction

The results of SwissADME analysis for the three compounds isolated from ginger, namely[8]-gingerol, [6]-paradol, shogaol, and panduratin (positive control), showed drug-likeness parameters, as shown in Table 3. The results of Protox-II are presented in Table 4, which shows the level of toxicity in rodents from the three ginger isolates, namely, [8]-gingerol, [6]-paradol, shogaol, and panduratin A positive control. The parameters observed were the LD_{50} and hepatotoxicity. The prediction results showed that panduratin A, as a positive control, had an LD_{50} dose of 2000 mg/kg and was mildly toxic.

The other parameters observed in this study were the pharmacokinetic profile evaluation (ADME) and drug likeness. These parameters are required to determine the physicochemical properties of the drug, an overview of whether the drug is designed in oral preparations, and its similarity to the drug. ADME and drug-likeness evaluation in silico was carried out using the SwissADME web tool developed by the Swiss Institute of Bioinformatics and can be accessed for free at http://www.swissadme.ch/. The parameters observed for the drug-likeness assessment used five Lipinski rules: molecular weight (g/mol), log. octanol/water partition coefficient, Hydrogen Bond Donor (HBD), Hydrogen Bond Acceptor (HBA), and Total Polar Surface area (TSPA).

Table 3. Results from SwissADME for 3 compounds of *Zingiber officinale*

Compound	Molecular weight (g/mol)	Log P	Hydrogen Bond Donor (HBD)	Hydrogen Bond Akseptor (HBA)	Total Polar Surface Area (TSPA Å²)	*Rotable Bond*	*Druglikeness*
8-Gingerol	322.44	3.87	2	4	66.76	12	Yes Score: 0.55
6-Paradol	278.39	3.96	1	3	46.53	10	Yes Score: 0.55
Shogaol	276.37	3.76	1	3	46.53	9	Yes Score: 0.55
Panduratin A (positive control)	406.522	4.76	2	4	66.76	6	Yes Score: 0.55
Parameter *Rule of five*	<500	<5	<5	<10	<140	-	-

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Table 4. Results from Protox II for 3 compounds of *Zingiber officinale*

Nama Senyawa	LD_{50}	Hepatoksisitas
8-Gingerol	250 mg/kg	No P = 0.83
6-Paradol	2580 mg/kg	No P = 0.71
Shogaol	687 mg/kg	No P = 0.72
Panduratin A (Kontrol Positif)	2000 mg/kg	No P = 0.63

The molecular weight of the drug plays a role in determining the bioavailability of drugs made in oral preparations; however, the molecular weight limit of 500 Da does not significantly classify compounds into good or poor oral bioavailability[22]. Poor determination of bioavailability occurs if more than two drug-like parameters violate the five Lipinski rules. Based on ADME profiling using SwissADME, the three ginger plant isolates and the positive control had a molecular weight of <500 g/mol.

The octanol/water partition coefficient (LogP) is defined as the ratio of the concentration of a chemical in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. The parameters were measured using a low solute concentration, where Kow is a very weak function of the solute concentration. LogP values are usually measured at room temperature (20 or 25°C). The effect of temperature on LogP is not large, usually in the range of 0.001–0.0 Iog Kow units per degree, and can be either positive or negative. In addition, the LogP value for all ginger plant isolates was 3.76 to 3.96, while the positive control (Panduratin A) had a LogP value of 4.76. This shows that the three compounds derived from ginger plant isolates have better solubility levels than panduratin A as a positive control[22].

Hydrogen bonds are divided into hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA). HBD is a bond or molecule that supplies hydrogen atoms from hydrogen bonds. HBD bonds are generally less polar than the HBA bonds. HBA is an electronegative atom of a neighboring molecule or ion that contains an electron pair that participates in hydrogen bonding. All compounds of the ginger isolates and positive controls in this study met the following criteria: HBD <5 and HBA <10. The Total Polar Surface Area (TPSA) value indicates the level of absorption in the intestine. All compounds of the ginger plant isolates and positive controls showed good absorption, with a TPSA <140.

A robust bond is the number of bonds that can freely rotate around it. This bond is defined as a single bond rather than a bond in the ring attached to a nonterminal heavy atom. Lipinski's rule of five limits the number of twistable bonds to less than 10 (RB < 10) for drug candidates. Based on the results of this study, only Shogaol fulfilled these rules, with a rotable bond value of 9. However, all compounds met the drug-likeness parameter because the other five rules fulfilled the SwissADME results listed in Table 3.

Toxicity prediction of compounds was carried out using the ProTox-II web tool, which can be accessed for free at https://tox-new.charite.de/protox_II/. This evaluation aimed to predict the safety level of orally administered drug compounds.

The median lethal dose (LD50) value provides information about the toxic fragments of three active compounds, namely]8]-gingerol, shogaol, and [6]-paradol. Based on the results of the study, it was shown that the compounds [8]-gingerol, [6]-paradol, shogaol, and the

positive control panduratin A had LD_{50} values of 250 mg/kg, 2580 mg/kg, 687 mg/kg, and 2000 mg/kg, respectively. In this case, [8]-gingerol had a more toxic effect than the other compounds because of its low LD_{50} value. Hepatotoxicity indicates the degree of damage caused by a compound to an organ. Compounds that can induce significant hepatotoxicity can cause liver damage, which is one of the major reasons for the sale of drugs on the market[23]. Prediction of drug-induced liver injury (DILI) is an important parameter that is safe for drug development, regulators, and midwives[24, 25]. The prediction of hepatotoxicity using ProTox-II has been validated with an accuracy rate of 82–86%. The prediction results of this study are presented in Table III, which shows that none of the tested compounds occurred or were inactive. So it can be concluded that panduratin A, [8]-gingerol, shogaol, and [6]-paradol are safe to use and do not damage the liver. These results are in accordance with those reported by Lukiati et al.[26, 27], who predicted the toxicity of compounds [8]-gingerol, shogaol, and [6]-paradol without hepatotoxicity.

Conclusions

Three ginger compounds from database [8]-gingerol, [6]-paradol, and shogaol, showed potential as DEN2 NS2B/NS3 inhibitors. The results of physicochemical and toxicity profile tests showed that only [8]-gingerol had drug-like properties and a moderate level of toxicity. However, further study is needed to determine bioactivity of gingerol by *in vitro* and *in vivo* studies.

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