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Inhibitory effect of Sinapic acid derivatives targeting structural and non-structural proteins of dengue virus serotype 2: An in-silico assessment

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ABSTRACT

DENV infects 50–100 million individuals, and 500,000 of them go on to acquire the more serious dengue hemorrhagic fever, which causes around 20,000 fatalities every year. Despite its widespread nature, there is no medication licenced to treat this condition. The purpose of this work is to identify *anti*-DENV medicines from sinapic acid (SA) derivatives utilising in-silico evaluation through docking and pharmacokinetics investigations. For the DENV-2 envelop protein, 1-*O*-β-D-glucopyranosyl sinapate had a significant docking score of −7.7 kcal/mol, while sinapoyl malate had a docking score of −6.7 kcal/mol for the DENV-2 NS2B/NS3 protein. Additionally, according to the PASS server, 1-*O*-β-D-glucopyranosyl sinapate and sinapoyl malate have a wide range of enzymatic activities since their probability active (Pa) values is > 0.700. These compounds exhibit a numerous pharmacological effect through activating the body's enzymes, according to analyses of their pharmacokinetic qualities. Accordingly, these substances showed acute toxicity rates at LD50 log10 (mmol/g) and LD50 (mg/g) concentrations when administered via various routes, including intraperitoneal, intravenous, oral, and subcutaneous. The result of this research suggests, 1-*O*-β-D-glucopyranosyl sinapate and sinapoyl malate may function as possible inhibitors to halt the DENV, and more in-vitro and in-vivo research is required to validate their activity and other features.

1. Introduction

Mosquito-borne dengue virus (DENV) is a major global health problem that is prevalent in tropical and sub-tropical regions, mostly in urban and semi-urban environments. Dengue is currently a threat to around half of the world's population, with 100–400 million cases reported year (https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue). Although the majority of DENV infections are asymptomatic or only result in moderate sickness, on rare occasions, DENV can cause more serious instances, including fatalities. With four distinct but closely related serotypes, DENV is a genus of flavivirus and a member of the *Flaviviridae* family (Adawara et al., 2021). Dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) are all caused by different serotypes of DENV (Roney et al., 2021), however DENV-2 and DENV-3 are the most often reported viruses to cause significant disease (Balmaseda et al., 2006). A single polypeptide precursor including three structural proteins (C, pr-M, and E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) is encoded by the DENV genome, which is a positive-sense single--stranded RNA (Roney et al., 2023a,b). Despite the disease's widespread occurrence, there is still no FDA-approved medication available to treat it. Therefore, it is essential to find and create antiviral medications to combat DENV.

The viral envelope protein (E-protein) aids in the fusing of the membranes of the host cell and viral cells during receptor-mediated endocytosis. Consequently, E-protein is acknowledged as a significant protein target for the creation of antiviral medicines for DENV. While the serine protease activity is aided by the DENV N-terminal domain of

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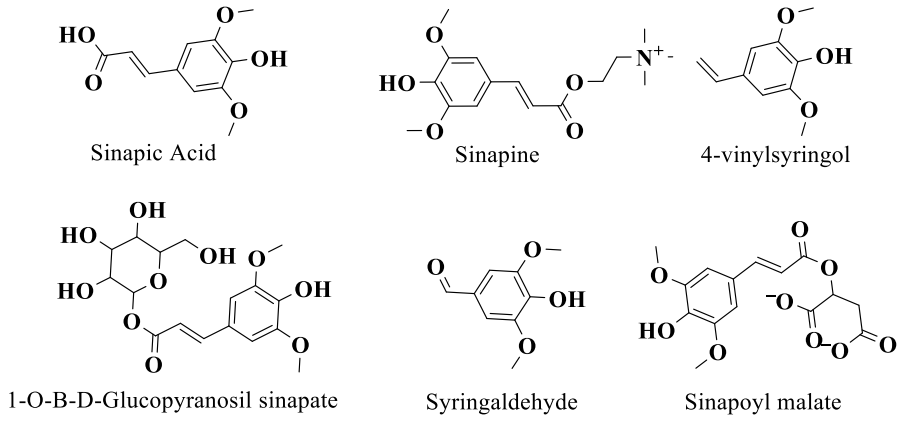

Fig. 1. SA and its derivatives.

NS3 and NS2B (Indu et al., 2021). The NS2B/NS3 pro complex is a complex structure that results from the interaction of NS3 and NS2B. This complex has the ability to break down viral proteins. Viral replication is hampered by any changes in this region's functional behaviour. NS2B/NS3 complex is therefore thought to be a crucial and significant target for the screening and evaluation of the effects of various pharmacological candidates (Qamar et al., 2017).

The 3,5-dimethoxy-4-hydroxycinnamic acid known as Sinapic acid (SA) can also be found in the form of esters, much like other hydroxycinnamic acids (Eroğlu et al., 2018). SA has been found in many different fruits, vegetables, cereal grains, oilseed crops, certain spices, and medicinal plants (Pandi and Kalappan, 2021). SA is a chemical that is commonly present in the plant world (Chen, 2016). Sinapoyl malate, which is often present in leaves, and sinapine (sinapoyl choline), which accumulates in roots, are the two main sinapoyl esters. Sinapoyl glucose (1-*O*-β-D-glucopyranosyl sinapate), which is present in all the diverse Brassicaceae species, is the most prevalent SA glycoside. Raw rapeseed oil contains 4-vinylsyringol, a decarboxylation byproduct of SA. SA undergoes structural modifications that lead to the synthesis of 4-vinylsyringol and syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde) under the increased temperature and pressure required to extract oil from oilseeds (Nićiforović and Abramovič, 2014).

SA is a naturally occurring phenolic acid that comes from cinnamic acid. It possesses antibacterial, anticancer, anti-inflammatory, antioxidant, and neuroprotective properties (Lee et al., 2021). SA is recognised to have a strong antioxidant activity (Galano et al., 2011) and it has anticancer benefits by lowering the levels of CDH2, MMP2, and MMP9 in human prostate cancer cells (Eroğlu et al., 2018). Additionally, SA contributes to anti-inflammatory effects by preventing the release of the cytokines IL-6 and IL-8 from the NF–B pathway (Zhang et al., 2017). *Salmonella enterica* and *Escherichia coli* are both known to be resistant to antibacterial actions of SA (Tesaki et al., 1998). SA showed a notably low cytotoxicity (CC_{50} = 189.3 μg/mL) and a half-maximal inhibitory concentration (IC_{50}) of 2.69 μg/mL, indicating a promising selective antiviral potential via in-vitro approaches against SARS-CoV-2 (Orfali et al., 2021a,b). Based on antiviral effectiveness of SA against SARS-CoV-2, we postulated that SA and its derivatives may interact with the structural and non-structural proteins of DENV-2. Therefore, we use an in-silico technique to define the mode of action of SA against DENV-2 in an approximate manner.

Viruses are now untreatable, and the medications that are available are costly and have unfavorable side effects. Six SA derivatives (Fig. 1) have been tested for their possible inhibitory effect against DENV-2 E-protein and DENV-2 NS2B/NS3 protease using an in-silico technique as a result of the paucity of antiviral medications. Since there hasn't been a single treatment developed to treat dengue illness up to this point, the current investigation was conducted to find an effective and promising therapeutic candidate.

2. Methodology

2.1. Recruitment of protein and ligand data

In order to determine the antiviral potential of SA derivatives against the structural and non-structural proteins of DENV-2, they were chosen as ligands from a published paper (Nićiforović and Abramovič, 2014). The viral proteins were also downloaded from the protein database as in crystalline form to dock with SA derivatives. The structural E-protein was downloaded from the protein data bank with the PDB id 1OKE (Modis et al., 2003), and the non-structural NS2B/NS3 protease was also downloaded with the PDB id 2FOM (Erbel et al., 2006). The 2D structure of SA derivatives was created in ChemSketch and stored in. mol format for docking with the target proteins. DENV-2 E-protein and NS2B/NS3 protease were downloaded as. pdb format for the docking with the selected ligands.

2.2. Molecular docking

The virtual screening approaches discussed earlier were utilised to estimate the docking analysis utilising the online docking application Cavity-detection guided Blind Docking (CB-Dock) (Padhi et al., 2021; Roney et al., 2023a,b). The CB-Dock programme was used to prepare the PBD file of the receptor and the. mol file containing the ligands for docking. Multiple top cavities were automatically chosen and used for additional docking analysis throughout this procedure (Liu et al., 2020). The first conformation is thought to be the optimum binding posture, while the area nearby is thought to be the question ligand's best binding site. The poses with the highest docking scores were chosen for further testing in comparison to the reference chemical Panduratin A after considering the binding modalities, interactions with active site residues, and docking score.

2.3. Physicochemical and pharmacokinetics analysis

To evaluate the therapeutic potential of the best docked molecules further accurately, the online SwissADME programme was used (Adawara et al., 2022). The SMILES file containing active compounds is all that is required for production; understanding of the active site or binding mechanism is not required.

2.4. Pharmacophore analysis

Structure-based and ligand-based techniques have been integrated with the energetic (e)-pharmacophore method (Samy et al., 2023). The

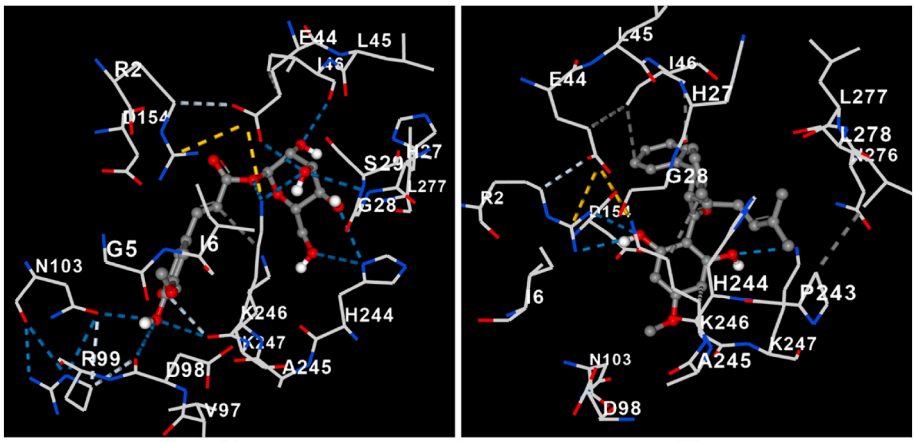

Fig. 2. Binding affinities among the residues of structural protein (PDB ID: 1OKE) of DENV-2 with (a) 1-*O*-β-D-Glucopyranosyl sinaoate and (b) Panduratin A. (Dash line showed the bound) (Blue color: hydrogen bonds; Sky blue color: weak hydrogen bonds color; Black: Hydrophobic interactions; Yellow color: ionic interactions). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Schrodinger PHASE module was used to determine the pharmacophore sites of lead compounds, including hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), positively ionizable (P), negatively ionizable (N), and aromatic ring (R) (Rani et al., 2023). The functional groups that are part of the targeted enzyme's bioactivity are included in the extracted pharmacophore hypothesis.

2.5. Drug probability

The Bayesian-based Prediction of Activity Spectra for Substances (PASS) was utilised to determine the antiviral potential of SA using the chemical's SMILES as inputs (Asiedu et al., 2021). Based on the structural-activity link between the chemical of interest and a training set of more than 26,000 compounds with known biological effects, PASS calculates the fundamental biological features of molecules. For a projected activity, the Pa and Pi that PASS predicts for each unique chemical range from 0.000 to 1.000. When Pa >0.3 and Pa > Pi for a certain medication activity, it is interesting to study the pharmacological activity (Kwofie et al., 2021).

2.6. Rat acute toxicity

The in-silico acute toxicity was predicted utilising the online tool GUSAR (General Unrestricted Structure-Activity Relationships) (Madduluri and Sah, 2020). The GUSAR programme predicts toxicity using a collection of software that includes a database of more than 10,000 chemical substances. Quantitative structure activity relationship (QSAR) analysis was used to forecast the median lethal dosage (LD50) of the chemical agent (log10 mg/kg). The analysis considers the many different ways of delivery, including intraperitoneal, intravenous, subcutaneous, and oral (Raheem et al., 2023).

3. Results and discussion

3.1. Molecular docking

To determine if the SA derivatives had the potential to be dengue antagonists, they were docked with the structural (E-protein) and non-structural (NS2B/NS3 protein) proteins of DENV-2 in this work. In order to determine if these compounds have anti-dengue potential, the present study looked at three docking outcomes, including cavity size, docking score, and ligand-target interactions. According to the results looked at, the current study found that Sinapoyl malate and 1-*O*-β-D-Glucopyranosyl sinaoate had the greatest docking scores and energy values against E-protein and NS2B/NS3 protein, respectively. In addition, among the investigated SA derivatives, these substances are also known to form strong hydrogen bonds with the target proteins' amino acid residues.

Despite having moderate docking scores, other SA derivatives also exhibited hydrogen bonding, hydrophobic and ionic connections with these DENV-2 proteins (Tables S1 and S2) which indicated that these compounds also showed *anti*-DENV-2 activity. The binding score and hydrogen bond interactions of the docked complex in the current investigation were evaluated and compared to those of the reference molecule Panduratin A. Panduratin A showed the strongest suppression of DENV-2 NS2B/NS3 protease cleavage, with 65% inhibition at 80 ppm (parts per million) concentration (Kiat et al., 2006). It showed competitive inhibition against DENV-2 NS2B-NS3pro with the IC_{50} value of 56 μM (Hariono et al., 2019). According to Frimayanti et al. (2011), it interacted with His 51, Asp 75, Ser 135 and Gly 153 and had a strong binding affinity (−11.27 kcal/mol) towards the active site of DENV-2 NS2B/NS3. In addition, it exhibited a single hydrogen bonding interaction with the DENV-2 E-protein active site (Lavanya et al., 2015).

3.2. Docking analysis of structural (E-protein) protein (1OKE)

The cavity size of 380 gives a superior docking score of −7.7 kcal/mol for 1-*O*-β-D-glucopyranosyl sinaoate (Table S1). In-depth research has been done on this docked complex to better understand how 1-*O*-β-D-Glucopyranosyl Sinaoate interacts with the amino acids of the DENV-2 structural protein (E-protein). During the analysis of the docked complex, it was discovered that 1-*O*-β-D-Glucopyranosyl Sinaoate and envelop protein made contact along around three lines, as will be explained below.

i. The hydrogen bond interactions between 1-*O*-β-D-Glucopyranosyl sinaoate and envelop protein were Ile46, Glu44, His 244, Lys246, Asp 98 and Asn 103 (Fig. 2a and Table S1).
ii. Besides the hydrogen bond interactions, hydrophobic interactions have also formed between them with the residues of Glu44 and Lys246 (Fig. 2a and Table S1).
iii. Besides the hydrogen bonds and hydrophobic interactions, ionic interactions with residues of Arg2 and Lys246 can be found precisely in the interaction map (Fig. 2a and Table S1).

The reference substance Panduratin A, on the other hand, docks in the same cavity with a docking score of −7.7 kcal/mol. With the Glu44 residue as well as the Ile46, Glu44, Lys246 and Leu 278 residues,

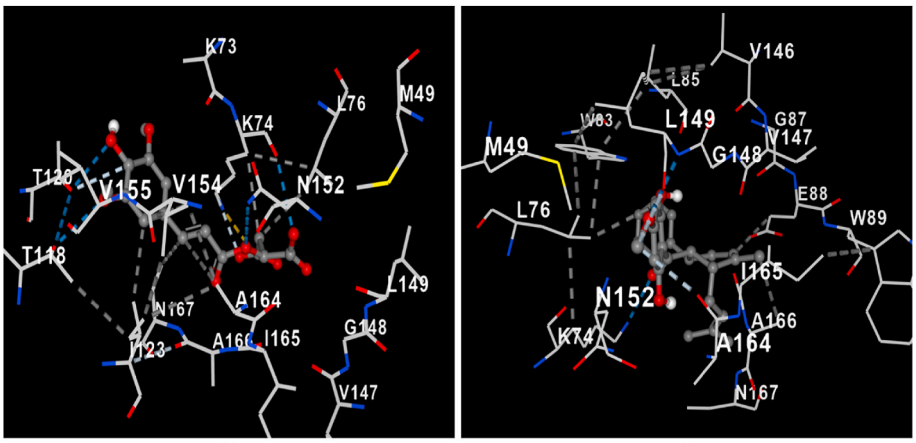

Fig. 3. Binding affinities among the residues of non-structural protein (PDB ID: 2FOM) of DENV-2 with (a) Sinapoyl malate and (b) Panduratin A. (Dash line showed the bound) (Blue color: hydrogen bonds; Sky blue color: weak hydrogen bonds; Black color: Hydrophobic interactions; Yellow color: ionic interactions). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Physicochemical and pharmacokinetics analysis of 1-*O*-β-D-Glucopyranosyl sinaoate and Sinapoyl malate.

C. Name	MW	HA	HD	MR	TPSA	HIA	BBB	1A2	2C19	2C9	2D6	3A4	SP
Reference Value	≤500	≤10	≤5	≤120	75-140 Å^2	High	No	No	No	No	No	No	–
1-*O*-β-D-Glucopyranosyl sinaoate	386.35 g/mol	10	5	90.09	155.14 Å^2	Low	No	No	No	No	No	No	−8.90 cm/s
Sinapoyl malate	340.28 g/mol	9	3	80.40	139.59 Å^2	High	No	No	No	No	No	No	−7.73 cm/s

MW: molecular weight, HA: hydrogen bond acceptor, HD: hydrogen bond donor, MR: molar refractivity, TPSA: topological polar surface area, HIA: human intestine absorption, BBB: blood brain barrier, 1A2 to 3A4: CYP450 enzyme.

Panduratin A displayed a hydrogen bond interaction. The ionic interactions between Lys246 and Arg2 residues and Panduratin A were also demonstrated (Fig. 2b and Table S1).

3.3. Docking analysis of non-structural (NS2B/NS3) protein (2FOM)

With a cavity size of 912, sinapoyl malate docks with a score of −6.7 kcal/mol (Table S2). The interaction between Sinapoyl malate and the amino acids of the DENV-2 non-structural protein (NS2B/NS3 protein)

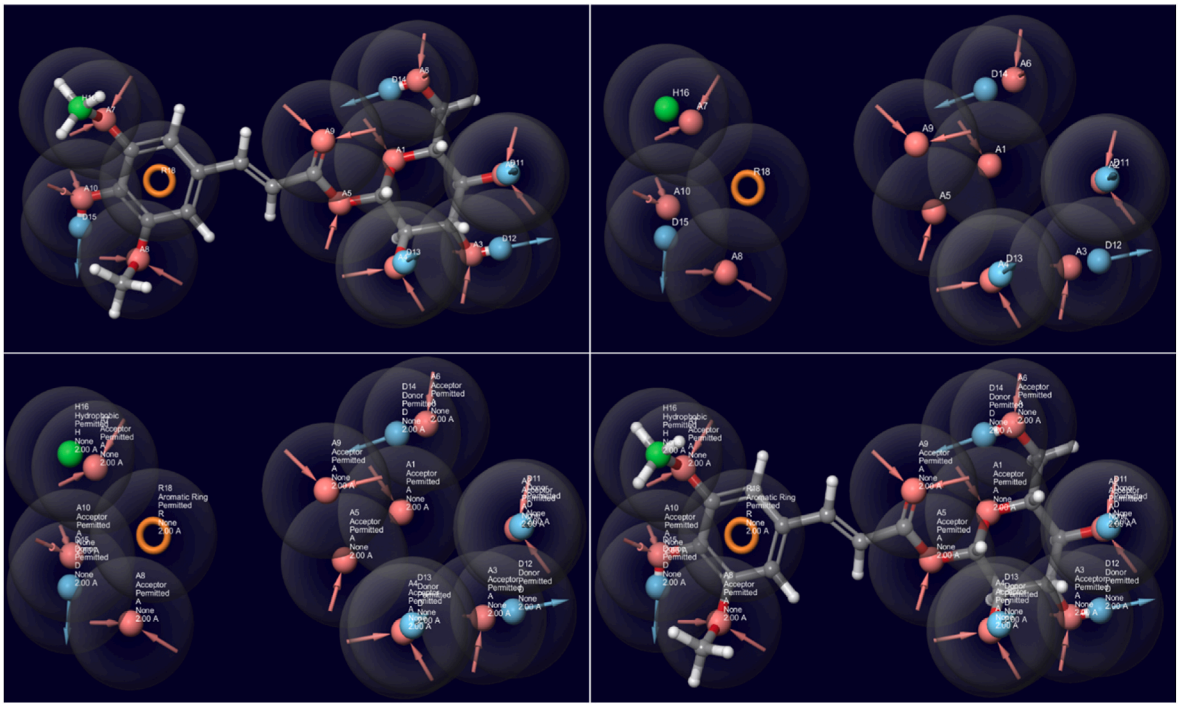

Fig. 4. Pharmacophore hypothesis of 1-*O*-β-D-glucopyranosyl sinaoate. (Orange color: HB Acceptor, Blue color: HB Donor; Green color: Hydrophobic; Yellow color: Aromatic ring). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

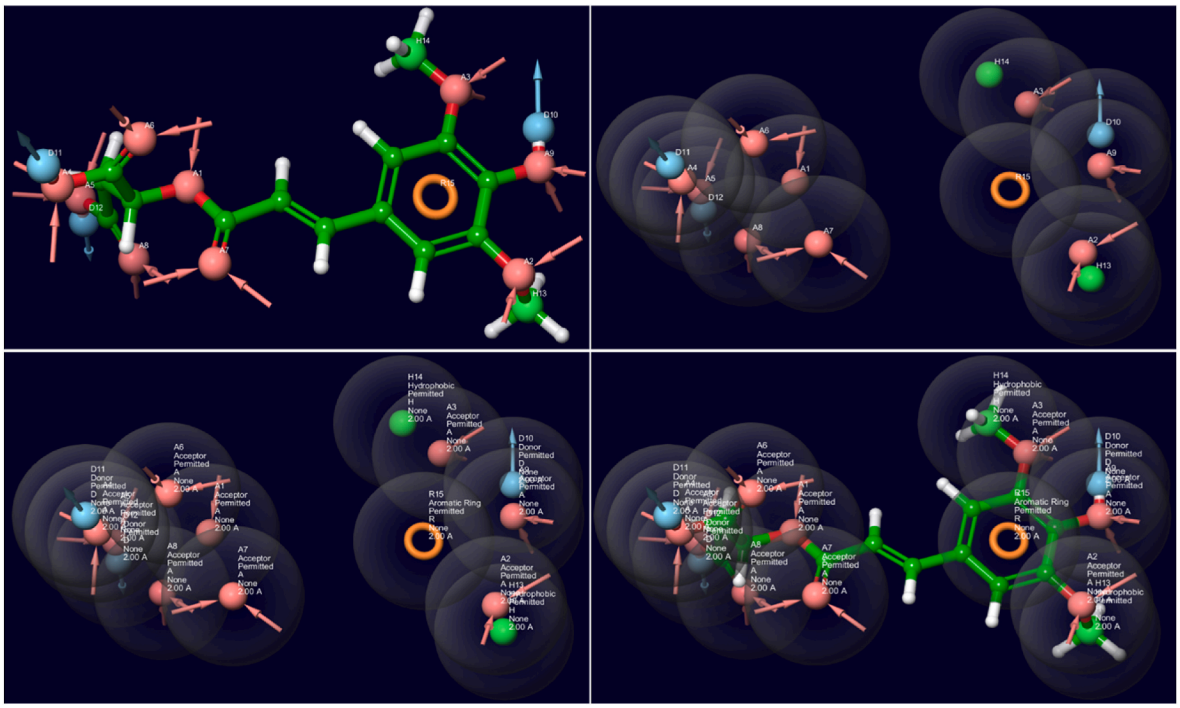

Fig. 5. Pharmacophore hypothesis of Sinapoyl malate. (Orange color: HB Acceptor, Blue color: HB Donor; Green color: Hydrophobic; Yellow color: Aromatic ring). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

has also been thoroughly explored in this docked complex. During the analysis of the docked complex, it was discovered that Sinapoyl malate and the NS2B/NS3 protein made contact along around three lines, as will be explained below.

i. The hydrogen bond interactions between Sinapoyl malate and NS2B/NS3 protein were Thr120, Lys74, Ala164, Ile165, Ala166 (Fig. 3a and Table S2).
ii. Besides the hydrogen bond interactions, hydrophobic interactions have also formed between them with the residues of Leu76, Lys74, Ala164, Val 154, Ile 123 and Thr118 (Fig. 3a and Table S2).
iii. Besides the hydrogen bonds and hydrophobic interactions, ionic interaction with residue of Lys74 can be found precisely in the interaction map (Fig. 3a and Table S2).

The reference substance Panduratin A, on the other hand, has a docking score of −7.0 kcal/mol in the same cavity. In addition to hydrophobic interactions with Lys74, Leu76, Trp 83, Leu 85, Ala166, Glu 88, and Trp 89 residues, Panduratin A displayed hydrogen bond interactions with the Ile165 and Asn 167 residues (Fig. 3b and Table S2).

3.4. Physicochemical and pharmacokinetics analysis

The physicochemical characteristics, including molecular weight (MW), molar refractivity (MR), topological polar surface area (TPSA), hydrogen bond acceptors (HA), donors of hydrogen bonds (HD), and others, were displayed in Table 1. All of these compounds met the criteria, with the exception of 1-*O*-β-D-Glucopyranosyl sinaoate, whose TPSA was somewhat greater.

The blood brain barrier (BBB) and human intestinal absorption (HIA) are important characteristics for the distribution and absorption of drugs, respectively (Shen et al., 2010). While 1-*O*-β-D-Glucopyranosyl sinaoate has a low HIA, sinapoyl malate has a high absorption level by the human gut. Additionally, these substances had harmful outcomes in BBB, which is a strong indication that they can function as drugs. The CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 isoforms of the CYP450 enzyme family are key players in drug metabolism. The first and most important isoform is CYP3A4, which has an intestine and kidney and is responsible for 50% of the drug's metabolism. The CYP2D6 isoform follows CYP3A4, which is involved in 20% of drug metabolism. Additionally, 15%, 12%, and 11%, respectively, of drug metabolism is carried out by the isoforms CYP2C9, CYP2C19, and CYP1A2 (Roney et al., 2021). It is crucial to understand whether the potential medication may inhibit a particular CYP enzyme isoform. Good medicines are those that do not develop antagonistic interactions with all CYP isoforms. Different CYP inhibitor models were developed for the case of metabolism, and the results suggest that these active substances are not CYP enzyme inhibitors. Our findings overwhelmingly support the notion that 1-*O*-β-D-glucopyranosyl sinaoate and sinapoyl malate are promising candidates for the creation of potent anti-dengue drugs.

3.5. Pharmacophore analysis

The generic pharmacophore theories were included in the 1-*O*-β-D-glucopyranosyl sinaoate and sinapoyl malate binding domain due to its high survival value in terms of its four features (Fig. 4). Additionally, the e-pharmacophore demonstrates that the 1-*O*-β-D-glucopyranosyl sinaoate comprises ten acquired acceptors (A1-A10), five obtained donors (D11-D15), one obtained negative ion (H16), and one obtained aromatic ring (R18). Sinapoyl malate furthermore includes nine acquired acceptors (A1-A9), three obtained donors (D10-D12), two obtained negative ionic (H13–H14), and one obtained aromatic ring (R15) (Fig. 5).

3.6. Druggability

Only the most likely pharmacological activities were included in Table S3 for 1-*O*-β-D-Glucopyranosyl sinaoate and Table S4 for Sinapoyl malate, according to the PASS server, which demonstrated that both compounds have a wide range of pharmacological possibilities. The probability active (Pa) score for these compounds ranges from 0.700 to

Table 2
Acute toxicity prediction of 1-*O*-β-D-Glucopyranosyl sinaoate and Sinapoyl malate.

Compound Name	Parameter	LD50 (mg/kg)			
		IP	IV	Oral	SC
1-*O*-β-D-Glucopyranosyl sinaoate	Log10 (mmol/kg)	0,309	−0,150	0747	0,495
	LD50 (mg/kg)	787,900	273,600	2156,000	1208,000
	Class	5	4	5	5
Sinapoyl malate	Log10 (mmol/kg)	0,625	−0,082	1038	0,469
	LD50 (mg/kg)	1434,000	282,000	3712,000	1001,000
	Class	Non-toxic	4	5	5

IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration.

0.956. These high Pa scores indicate a strong likelihood of pharmacological activity for both 1-*O*-β-D-Glucopyranosyl sinaoate and Sinapoyl malate. The diverse range of potential pharmacological activities suggests that these compounds could be valuable in various therapeutic applications.

3.7. Rat acute toxicity

In order to ascertain the negative consequences that can arise from unintentional or purposeful short-term exposure, a substance's acute toxic potential must be assessed (Yadav and Rohane, 2021). For long-term toxicity studies and other animal-based investigations (including human research), dose selection is based on the prediction of acute toxicity testing (Walum, 1998; Barlow et al., 2002). The findings of an acute toxicity test can be used to evaluate the toxicity status of the test chemical.

The PASS online tool was used to forecast the in-silico toxicity of the chosen lead compounds. The applicability domain (AD) of the QSAR models was found to include the bulk of the leads. The IV, oral, subcutaneous, and intraperitoneal routes were all taken into account in Table 2's toxicity estimates, which showed that all of the drugs fall within class 5. The chemicals were safe and essentially innocuous, according to the study.

4. Conclusion

Due to the high morbidity rate of dengue infection worldwide, it affects people not just from underdeveloped nations but also from industrialised countries. Dengue affects about 50,000 individuals a year, with dengue hemorrhagic fever accounting for 10% of all occurrences. Despite the disease's widespread distribution, there is presently no medication for it. Therefore, the goal of the current study was to investigate the SA derivatives' possible antiviral properties. This study found that 1-*O*-β-D-Glucopyranosyl Sinaoate and Sinapoyl Malate had great docking values and exceptional interactions with NS2B/NS3 proteins and DENV-2 E-protein, respectively. These compounds exhibit a variety of pharmacological capabilities through activating the human body's enzymes, according to pharmacokinetic property evaluations. On the other hand, analysis of the pharmacokinetic characteristics revealed that it is less harmful to rats when administered by various routes at dosages of LD50 log10 (mmol/kg) and LD50 (mg/kg). In light of this, it can be said that 1-*O*-β-D-Glucopyranosyl Sinaoate and Sinapoyl Malate were promising lead molecules that performed better than the reference compound against the DENV-2 E protein and NS2B/NS3 proteins, respectively. However, further in-vitro and in-vivo experiments are required to validate the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amolm.2023.100028.

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