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RESEARCH ARTICLE

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3,3-dimethyl-octane from *Physalis peruviana* as promising anti-DENV via ADMET prediction of pkCSM open webserver

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Abstract

Dengue is caused by the dengue virus (DENV) and being prevalent in 100 tropical and subtropical countries including Indonesia. This disease is spread by *Aedes* mosquitoes. There is currently no clinically authorized medicine to treat the dengue fever. *Physalis peruviana* has ethnomedicine application and noted for its antioxidant activities. This study purpose to investigate the pharmacokinetics or ADMET of anti-DENV from leaf parts of *P. peruviana*. The phytoconstituents data were gathered from multiple sources. The drug property and ADMET prediction were assessed using pkCSM. Following online screening, 3,3-dimethyl-octane functioned as predictive anti-DENV therapeutic candidate. Further dry and wet lab studies are needed to validate this finding.

Keywords: 3,3-dimethyl-octane, *Physalis peruviana*, Dengue fever, DENV, Dengue

Introduction

Dengue is caused by the dengue virus (DENV) and being endemic in 100 tropical and subtropical countries in Southeast Asia, Africa, America, and certain European areas[1]. This disease is transmitted by *Aedes* mosquitoes[2]. Based on WHO data, dengue cases declined slightly during the COVID-19 pandemic between 2020 and 2022. However, considerable in dengue cases have been reported globally by a significant increase, simultaneous occurrence of multiple outbreaks, and extending into previously unaffected regions[3]. Nowadays, there are no clinically approved anti-dengue for curing the infections

and treatment remains on curative care like as fluid replacement and analgesic use[4]. There are some anti-DENV therapeutic candidates like chloroquine, lovastatin, celgosivir, and prednisolone but have been failed to appreciably reduce viremia[5–7].

Physalis peruviana (Solanaceae) is a weed plant originated to America's Andes. This plant is widely adapted to a variety of altitudes, soils, and climatic conditions[8]. In Indonesia, the fruits of plant are consumed and restricted used as ethnomedicine in numerous ethnic due to its phytoconstituents[9–11]. However, no records found of *P. peruviana* screened as anti-DENV before particularly from its leaves. These phytoconstituents can be utilized to be simulated by pharmacokinetics using absorption, distribution, metabolism, excretion, and toxicity (ADMET) approaches. Thus, the objective of this study was to investigate the pharmacokinetics derived from *P. peruviana* leaves.

Materials and methods

Study area

This study conducted using *P. peruviana* phytoconstituents from the leaf portions from online database[8]. SMILES of the compounds were copied to identify the ADMET in open webserver. Selected phytoconstituents would be proposed as prospective treatment of dengue fever.

Procedures

The compounds contained in leaves of *P. peruviana* were retrieved from the KNApSAcK, Human Metabolite Database (HMDB), and ChemSpider. The information retrieved from this database included of code of identifier (CID), 3D structure, and simplified molecular-input line-entry system (SMILES). Selected compounds obtained from the database were tested using pkCSM to determine the pharmacological properties and pharmacokinetics. Threshold of drug-likeness prediction was set "yes" in all categories. On the other hand, pharmacokinetics was identified using selected ADMET identifiers from each classification. The threshold of these phases is written on **Table 1**. All filtered phytoconstituents will be recommended as prospective anti-DENV drugs[12,13].

Table 1. Distribution of drug properties and ADME predictors in pkCSM[14]

Parameter	Predictor	Unit	Requirement value
Drug properties	Molecular weight (MW)	Da	≤500
	Log of partition (LogP)	-	≤5
	Rotatable bond (RB)	-	≤10
	Hydrogen bond acceptor (HBA)	-	≤10
	Hydrogen bond donor (HBD)	-	≤5
	Surface area	Å	≤140
Absorption	Water solubility (A1)	log mol/L	-
	Caco-2 permeability (A2)	log Papp in 10^{-6} cm/s	>0.9
	Intestinal absorption (human) (A3)	% Absorbed	>30%
	Skin permeability (A4)	log Kp	≥-2.5
	P-glycoprotein substrate (A5)	Yes/No	-
	P-glycoprotein I inhibitor (A6)	Yes/No	-
	P-glycoprotein II inhibitor (A7)	Yes/No	-
Distribution	VDss (human) (D1)	log L/kg	≥-0.15
	Fraction unbound (human) (D2)	Fu	-

	BBB permeability (D3)	log BB	≥-1
	CNS permeability (D4)	log PS	≥-3
Metabolism	CYP2D6 substrate (M1)	Yes/No	-
	CYP3A4 substrate (M2)	Yes/No	-
	CYP1A2 inhibitor (M3)	Yes/No	-
	CYP2C19 inhibitor (M4)	Yes/No	-
	CYP2C9 inhibitor (M5)	Yes/No	-
	CYP2D6 inhibitor (M6)	Yes/No	-
	CYP3A4 inhibitor (M7)	Yes/No	-
Excretion	Total clearance (E1)	log mL/min/kg	Higher is better
	Renal OCT2 substrate (E2)	Yes/No	-
Toxicity	AMES toxicity (T1)	Yes/No	-
	Maximum tolerated dose (human) (T2)	log mg/kg/day	Higher is better
	hERG I inhibitor (T3)	Yes/No	-
	hERG II inhibitor (T4)	Yes/No	-
	Oral rat acute toxicity (T5)	mol/kg	Higher is better
	Hepatotoxciity (T6)	Yes/No	-

Data analysis

Data analysis conducted by reviewing each predictor using the recruitment value. Selected phytoconstituents would be passed to the next steps.

Results

Based on the literature review, there were 22 phytoconstituents found in leaves of *P. peruviana*. Those compounds were evaluated in KNApSAcK, HMDB, and ChemSpider to determine the CID and SMILE. However, just remains 19 compounds left on the databases (**Table 2**).

Table 2. Phytoconstituents from leaves of *P. peruviana*

Constituents	CID	Source	SMILE
(S)-4-Iodo-1,2-epoxybutane	-	-	-
1,1,1,5,7,7,7-Heptamethyl-3,3	-	-	-
1,2-Benzenedicarboxylic acid	C00055600	KNApSAcK	OC(C1=CC=CC=C1C(O)=O)=O
3,3-Dimethyl-hexane	HMDB0031418	HMDB	CCCC(C)(C)CC
3,3-Dimethyl-octane	121758	ChemSpider	CCCCCC(C)(C)CC
Campesterol	151215	ChemSpider	C[C@H](CC[C@@H](C)C(C)C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C
Diethyl ester	7478	ChemSpider	CCOC(=O)OCC
Docosane	HMDB0061865	HMDB	CCCCCCCCCCCCCCCCCCCCCC
Eicosamethylcyclodecasiloxane	453230	ChemSpider	C[Si]1(O[Si](O[Si](O[Si](O[Si](O[Si](O[Si](O[Si](O[Si](O1)(C)C)(C)C)(C)C)(C)C)(C)C)(C)C)(C)C)(C)C)C
Ethyl isoallocholate	-	-	-

Hexadecanoic acid	960	ChemSpider	CCCCCCCCCCCCCCCC(=O)O
Hexahydrofarnesyl acetone	9979	ChemSpider	CC(C)CCCC(C)CCCC(C)CCCC(=O)C
Linoleic acid	HMDB0000673	HMDB	CCCCC\C=C/C\C=C/CCCCCCCC(O)=O
Perulactone B	HMDB0030119	HMDB	CC1C(CC(O)C(C)(O)C2(O)CCC3(O)C4CC=C5CC=CC(=O)C5(C)C4CCC23C)COC1=O
Physalin B	HMDB0030128	HMDB	CC12OC(=O)C3(O)CCC4C(CC=C5CC=CC(=O)C45C)C45OC13C(C4=O)C1(C)CC2OC(=O)C1CO5
Physalin D	HMDB0034353	HMDB	CC12OC(=O)C3(O)CCC4C(CC(O)C5(O)CC=CC(=O)C45C)C45OC13C(C4=O)C1(C)CC2OC(=O)C1CO5
Physalin F	HMDB0034092	HMDB	CC12OC(=O)C3(O)CCC4C(CC5OC55CC=CC(=O)C45C)C45OC13C(C4=O)C1(C)CC2OC(=O)C1CO5
Phytol	HMDB0002019	HMDB	CC(C)CCC[C@@H](C)CCC[C@@H](C)CCC\C(C)=C\CO
Stigmasterol	HMDB0000937	HMDB	[H][C@@]1(CC[C@@]2([H])[C@]3([H])CC=C4C[C@@H](O)CC[C@]4(C)[C@@]3([H])CC[C@]12C)[C@H](C)\C=C\[C@@H](CC)C(C)C
Vitamin E	HMDB0001893	HMDB	CC(C)CCC[C@@H](C)CCC[C@@H](C)CCC[C@]1(C)CCC2=C(C)C(O)=C(C)C(C)=C2O1
Withanolide E	266675	ChemSpider	CC1=C(C(=O)O[C@H](C1)[C@@](C)([C@@]2(CC[C@@]3([C@@]2(CC[C@H]4[C@H]3C[C@@H]5[C@]6([C@@]4(C(=O)C=CC6)C)O5)C)O)O)O)C
Withanolide F	23332408	ChemSpider	CC1=C(C(=O)O[C@H](C1)[C@@](C)([C@@]2(CC[C@@]3([C@@]2(CC[C@H]4[C@H]3CC=C5[C@@]4(C(=O)CC=C5)C)C)O)O)O)C

Constituents who met all of the criteria in this screening advanced to the next round of filtering. Satisfied phytoconstituents suggest the drug-likeness structures of Lipinski, Ghose, Egan, Veber, and Muegge rules[15]. Additionally, several selected constituents with acceptable pharmacokinetics and toxicity were indicated as anti-DENV drug candidates (**Table 3**).

Table 3. Drug-likeness identification

Constituents	MW	LogP	RB	HBA	HBD	SA	Status
1,2-Benzenedicarboxylic acid	166.32	1.083	2	2	2	68.073	√
3,3-Dimethyl-hexane	114.232	3.2227	3	0	0	53.294	√
3,3-Dimethyl-octane	142.286	4.0029	5	0	0	66.024	√
Campesterol	400.691	7.6347	5	1	1	7.6347	×

Diethyl ester	118.132	1.1794	2	3	0	48.588	√
Docosane	310.61	8.8282	19	0	0	142.403	×
Eicosamethylcyclodecasiloxane	741.55	7.184	0	10	0	256.079	×
Hexadecanoic acid	256.43	5.5523	14	1	1	113.169	×
Hexahydrofarnesyl acetone	268.485	6.0145	12	1	0	121.105	×
Linoleic acid	280.452	5.8845	14	1	1	124.520	×
Perulactone B	488.621	2.4514	4	7	4	206.798	×
Physalin B	510.539	1.557	0	9	1	213.061	×
Physalin D	544.553	-0.2774	0	11	3	223.339	×
Physalin F	526.538	0.7682	0	10	1	217.859	×
Phytol	296.539	6.3641	13	1	1	133.778	×
Stigmasterol	412.702	7.8008	5	1	1	186.349	×
Vitamin E	430.717	8.84026	12	2	1	192.727	×
Withanolide E	486.605	2.7544	2	7	3	206.111	×
Withanolide F	470.606	3.5432	2	6	3	201.314	×

The pkCSM utilization is a way to estimate and improve the pharmacokinetics characteristics of small constituents according to the distance-based graph signature. Otherwise, this application extends the cutoff for pharmacological process in order to characterize and predict their pharmacokinetics features[14].

Table 4. Absorption analysis results

Constituent	A1	A2	A3	A4	A5	A6	A7
1,2-Benzenedicarboxylic acid	-2.364	0.743	74.928	-2.735	No	No	No
3,3-Dimethyl-hexane	-3.598	1.395	94.512	-1.353	No	No	No
3,3-Dimethyl-octane	-4.927	1.393	93.566	-1.006	No	No	No
Diethyl ester	-0.112	1.725	100	-2.973	No	No	No

From absorption and distribution standpoints, 3,3-dimethyl-hexane and 3,3-dimethyl-octane produced the best results although diethyl ester showed the safest one according to the highest dose for T2 and T5 (**Table 4-5, and 7**). In addition, 3,3-dimethyl-octane had the highest prediction for overall clearance (E1) (**Table 5**). Overall, all filtered phytoconstituents from *P. peruvina* leaves performed well in metabolic aspects (**Table 6**).

Table 5. Distribution and excretion analyses results

Constituent	D1	D2	D3	D4	E1	E2
1,2-Benzenedicarboxylic acid	-1.997	0.485	-0.191	-2.542	-2.542	No
3,3-Dimethyl-hexane	0.273	0.483	0.739	0.739	1.352	No
3,3-Dimethyl-octane	0.409	0.365	0.778	-1.955	1.419	No
Diethyl ester	-0.221	0.728	-0.207	-2.803	0.696	No

Discussion

There are several aspects in pharmacokinetics analyses in pkCSM include 4 categories: absorption, distribution, metabolism, excretion, and toxicity. Water solubility, Caco-2 cells permeability,

gut absorption, skin permeability, and P-gps inhibitory are all key factors in oral delivery and absorption, skin delivery, and cell barriers (**Table 4**)[16–18]. Besides, consistent rate of medication, proportion to unbound to protein, and the ability of drugs to pass the blood brain barrier (BBB) and central nerve system (CNS) impact the drug efficacy diffusion (**Table 5**)[19]. In the results of the prediction of absorption and distribution yielded 3,3-dimethyl-hexane and 3,3-dimethyl-octane which are in accordance with the requirements (**Table 4 and 5**). Meanwhile, 1,2-benzenedicarbosylic acid and diethyl ester did not meet fulfillment in Caco-2 and skin permeability (A2 and A4) as well as VDss in human (D1).

Table 6. Metabolism analysis results

Constituent	M1	M2	M3	M4	M5	M6	M7
1,2-Benzenedicarboxylic acid	No	No	No	No	No	No	No
3,3-Dimethyl-hexane	No	No	No	No	No	No	No
3,3-Dimethyl-octane	No	No	No	No	No	No	No
Diethyl ester	No	No	No	No	No	No	No

Aside from absorption and distribution classifications, there are three remains categories for pharmacokinetics aspects of drug candidates. Metabolism is one of the important parts in medication. Cytochrome P450 (CYP450) is detoxifying enzyme present in the liver that has several isoforms. Many drugs have substrate or inhibitory activities against these enzymes; nonetheless, the completely interfering with pharmaceutical metabolism is thus not recommended[13]. No phytoconstituents were screened to be metabolized and inactivated in the liver (**Table 6**). Total clearance and the renal uptake transporter organic cation transporter 2 (OCT2) are vital aspects for drug removal from core compartments and renal clearance[14,20]. 3,3-dimethyl-octan projected to have the largest total clearance but 1,2-benzenedicaroxylic acid had the opposite with 1.419 and -2.542 log mL/min/kg. No screened substances inhibited towards renal OCT2 substrate (**Table 5**).

Table 7. Toxicity analysis results

Constituent	T1	T2	T3	T4	T5	T6
1,2-Benzenedicarboxylic acid	No	0.884	No	No	1.837	No
3,3-Dimethyl-hexane	No	0.811	No	No	1.863	No
3,3-Dimethyl-octane	No	0.608	No	No	1.739	No
Diethyl ester	No	1.131	No	No	2.219	No

Toxicity prediction illustrated no result for mutagenicity (AMES toxicity, T1), cardiac potassium channel (hERG I/II inhibitors, T3-4), and harmful activities to liver (hepatotoxicity, T6)12. The increased maximum tolerated dose (human, T2) value and oral rat toxicity (LD50, T5) are more likely to be safe as prospective dengue medication[12]. Thus, diethyl ester emerged as the most suitable candidate of toxicity aspects with human maximum tolerated dose of 1.131 log mg/kg/day and LD50 that was 2.219 mol/kg (**Table 7**).

Screening approach was based on the website predictors with a limited value to assess whether or not the pharmacokinetic profiles of phytoconstituents were satisfactory. However, 3,3-dimethyl-

octane accounted for the majority of recruitments according to the pkCSM projections and might be processed as anti-DENV drug candidates by *in silico*, *in vitro*, and *in vivo* pathways (**Figure 1**).

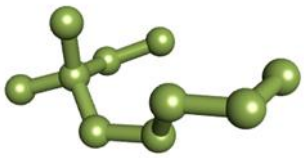

Figure 1. 3,3-dimethyl-octan in 3D structure

Conclusions

3,3-dimethyl-octane from leaves of *P. peruviana* exhibits promising prospective anti-DENV due to its capacity in ADMET prediction. Further *in silico*, *in vitro*, and *in vivo* analyses needed to validate this screening.

Acknowledgments

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Conflicts of Interest

There are not potential conflicts of interest.

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