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THE PREDICTION OF PHARMACOKINETIC PROPERTIES OF COMPOUNDS IN HEMIGRAPHIS ALTERNATA (BURM.F.) T. ANDER LEAVES USING PKCSM

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ABSTRACT

The inflammatory process has a role in the healing process and leads the body's homeostasis normal. Untreated acute inflammation can lead to organ pathology leading to a chronic inflammatory phenotype. Prediction of the affinity of 22 compounds in *Hemigraphis alternata* leaves as anti-inflammatory has been conducted for COX-1, COX-2 and 5-LOX. The Prediction of pharmacokinetic properties of the compounds was carried out to obtain inflammatory drug candidates that have high affinity with adequate ADME. The application used in this research is pkCSM, a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. The pkCSM used 20 predictors which were divided into 4 properties, absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors) and excretion (2 predictors). Based on the prediction results, there are 5 compounds that have the best pharmacokinetic properties, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural and 2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*. *3,7,11,15-Tetramethyl-2-hexadecen-1-ol* is a compound that is predicted to have high affinity as an anti-inflammatory and good ADME.

Keywords: Pharmacokinetic, *Hemigraphis alternata*, pkCSM.

INTRODUCTION

Inflammation is a protective reaction of the immune system to defend the body from potentially harmful stimuli, both infectious and non-infectious agents that cause cell damage. It induces the inflammatory cells to be active and trigger inflammatory signaling pathways. The inflammatory process has an important function in the healing process so that abnormal body homeostasis can be restored. Acute inflammation that is not treated properly can cause organ pathology to worsen and eventually lead to a chronic inflammatory phenotype [1–3].

Hemigraphis alternata has various medicinal properties, including anti-inflammatory, anti-nociceptive and anti-diarrhoeal activities. Methanol and ethyl acetate extract of *Hemigraphis*

alternata leaves has been shown to provide anti-inflammatory and non-toxic effects to mice [4]. There are 22 secondary metabolites that have been isolated in the leaves of this plant [5]. These compounds have predicted anti-inflammatory activity against COX-1, COX-2 and 5-LOX receptors. The compound predicted to have the highest affinity for COX-1 and COX-2 were *3,7,11,15-Tetramethyl-2-hexadecen-1-ol* [6]. Meanwhile, the compound predicted to produce the highest affinity for 5-LOX was *n-Hexadecanoic acid* [7].

The relationship of pharmacokinetic properties, toxicity, and potency greatly affect the effectiveness of a drug. Determining the pharmacokinetic profile of a compound is carried out to determine the absorption, distribution, metabolism, and excretion (ADME) properties [8]. The initial assessment of ADME properties will help pharmaceutical researchers to select the best drug candidates for development and reject drug candidates that have a low probability of success. The aim of the in silico prediction of ADME properties is the accurate prediction of the in vivo pharmacokinetic properties of potential drug molecules in humans using only virtual structures [9]. The purpose of this study was to predict the pharmacokinetic properties (ADME) of 22 compounds contained in *Hemigraphis alternata* leaves through an in silico study.

EXPERIMENTAL SECTION

Provide sufficient detail to allow the work to be reproduced, including Materials, Instrumentation, and procedures.

Materials

The SMILES format of 22 compounds contained in the leaves of *Hemigraphis alternata* was obtained from PubChem (pubchem.ncbi.nlm.nih.gov). Compounds that do not have the SMILES format in PubChem can be obtained by describing their structure in the Online SMILES Translator (https://cactus.nci.nih.gov).

Instrumentation

The prediction of pharmacokinetic properties of 22 compounds in the leaves of *Hemigraphis alternata* was conducted using pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction).

Procedure

pkCSM is based on general properties of compounds (molecular properties, toxicophores and pharmacophores) and distance-based graph signatures. In pkCSM there are 20 predictors that describe the pharmacokinetic properties of a compound. The predictors were divided into absorption of 7 predictors, distribution of 4 predictors, metabolism of 7 predictors and excretion of 2 predictors (**Table 1**) [8,10,11].

Table 1. Distribution of ADME predictors in pkCSM

Property	Predictor	Unit	Property	Predictor	Unit
Absorption	Water solubility (A1)	log mol/L	Distribution	CNS permeability (D4)	log PS
Absorption	Caco2 permeability (A2)	log Papp in 10-6 cm/s	Metabolism	CYP2D6 substrate (M1)	Yes/No
Absorption	Intestinal absorption (human) (A3)	% Absorbed	Metabolism	CYP3A4 substrate (M2)	Yes/No
Absorption	Skin Permeability (A4)	log Kp	Metabolism	CYP1A2 inhibitor (M3)	Yes/No
Absorption	P-glycoprotein substrate (A5)	Yes/No	Metabolism	CYP2C19 inhibitor (M4)	Yes/No
Absorption	P-glycoprotein I inhibitor (A6)	Yes/No	Metabolism	CYP2C9 inhibitor (M5)	Yes/No
Absorption	P-glycoprotein II inhibitor (A7)	Yes/No	Metabolism	CYP2D6 inhibitor (M6)	Yes/No
Distribution	VDss (human) (D1)	log L/kg	Metabolism	CYP3A4 inhibitor (M7)	Yes/No
Distribution	Fraction unbound (human) (D2)	Fu	Excretion	Total Clearance (E1)	log ml/min/kg
Distribution	BBB permeability (D3)	log BB	Excretion	Renal OCT2 substrate (E2)	Yes/No

In this study, virtual screening was carried out to obtain several compounds that had good ADME. Virtual screening is based on the results of the ADME predictor which has a numerical value with certain limitations. The predictors were Caco2 permeability (A2), intestinal absorption (human)

(A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3), CNS permeability (D4), total clearance (E1) [12]. The requirements are log Papp in 10-6 cm/s in Caco2 permeability (A2) > 0.9, intestinal absorption (human) (A3) > 30%, log Kp ≥ -2.5 in skin permeability (A4), log L/kg ≥ -0.15 in VDss (human) (D1), log BB ≥ -1 in BBB permeability (D3), log PS ≥ -3 in CNS permeability (D4).

The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54, 5 compounds with the best ADME were obtained. Subsequently, these results were compared with the predicted affinity in previous studies and 1 compound with good affinity and ADME was obtained [8].

RESULTS AND DISCUSSION

pkCSM is a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. pkCSM adapts the Cutoff Scanning concept to represent molecular and chemical structures to represent and predict their pharmacokinetic properties [8].

Water solubility is an important factor for a drug to show a better pharmacological response for oral administration. Drugs that have good water solubility properties will cause the drug to have good absorption and bioavailability properties. Good drug absorption and bioavailability can increase the plasma drug concentration at the target site to perform therapeutic functions [13].

Caco-2 cells are a cell line derived from colorectal adenocarcinoma [14]. The Caco-2 model was used to predict the possible gastrointestinal permeability of drugs in pre-clinical trials. This model expresses cytochrome P450 enzymes, transporters, microvilli, and enterocytes based on characteristics identical to those of the human small intestine [15]. The permeability of Caco-2 of a compound is high if it has a Papp > 8 x 10-6 cm/s. The permeability of Caco-2 is high if the predictive value is > 0.90 in the pkCSM predictive model [8].

The intestine is the main site for absorption of oral drugs. The compound is predicted to have low Intestinal absorption (human) if the value is < 30% [8]. The skin is the boundary between the internal and external body environment. Skin characteristics and properties can modify and affect drug delivery and toxicity [16]. A compound has a tendency to be skin permeable which is expressed by the skin permeability constant logKp (cm/hour). The logKp value of the compound > -2.5 indicates that the compound has low skin permeability [8].

Substrate P-glycoprotein is an ATP-binding cassette (ABC) transporter that functions as a biological barrier by removing toxins and xenobiotics from cells. P-glycoprotein I/II inhibitor is the ability of the compound to inhibit the transport of P-glycoprotein I and P-glycoprotein II. P-glycoprotein-mediated modulation of transport has significant pharmacokinetic implications for Pgp substrates. Inhibition of P-glycoprotein I or P-glycoprotein II can be exploited for certain therapeutic advantages or produce contraindications [8].

VDss (human) is the total amount of drug in the body divided by the total concentration of drug in plasma at steady state. This condition occurs when the system undergoes an infusion of the drug at a constant rate into the plasma and all drug concentrations in the body do not change [17]. VDss is low if the value is < 0.71 L/kg (log VDss < -0.15) and high if the value is > 2.81 L/kg (log VDss > 0.45). The effectiveness of a drug can be affected by the ability of the drug for binding proteins in the blood. The larger the fraction of the drug that is not bound to protein (fraction unbound), the more efficiently the drug will cross the cell membrane or diffuse [8].

Increased permeability of the BBB (Blood-Brain Barrier) which is a physical and biochemical barrier that plays a role in the defense of cerebral homeostasis can affect the pathological development of ischemic tissue [18,19]. A compound with a logBB > 0.3 can easily pass through BBB and a compound with a logBB < 1 is not well distributed to the brain. The ability of drug compounds to penetrate the CNS (Central Nervous System) can be determined from the value of the blood-brain permeability surface area product (logPS). This value was obtained from in situ brain perfusion with the compound directly injected into the carotid artery without any systemic distribution effect that could distort brain penetration. Compounds with logPS > -2 could penetrate the CNS, while compounds with logPS < -3 could not penetrate the CNS [8].

Cytochrome P450 is a detoxifying enzyme that can be found in the liver. Cytochrome P450 generally plays a role in drug metabolism. However, P450 inhibitors can dramatically alter drug pharmacokinetics. Therefore, it is important to know whether the given compound is a CYP2D6/CYP3A4 substrate predicted to be metabolized by P450. Cytochrome P450 oxidizes xenobiotics to be finally excreted. Many drugs are inactivated by cytochrome P450 and some can be activated by it. These enzyme inhibitors can affect drug metabolism and are contraindicated. It is therefore important to assess the ability of the compound to inhibit cytochrome P450 (isoform CYP1A2/CYP2C19/CYP2C9/CYP2D6/CYP3A4). A compound is considered a cytochrome P450 inhibitor if the concentration required to cause 50% inhibition is < 10 M [8].

Drug clearance is the volume of plasma in the vascular compartment that is cleared of drug per unit time. Total clearance is the sum of all body clearances. Total clearance gives an indication of drug elimination from the central compartment without reference to the mechanism of the process [20]. Organic Cation Transporter 2 (OCT2) is a renal uptake transporter that has an important role in the disposition and renal clearance of drugs or endogenous compounds. OCT2 substrates may cause adverse effects when administered concomitantly with OCT2 inhibitors [8].

In the results of the prediction of adsorption properties obtained compounds 3, 6, 9, 11, 13, 17, 19, 20, 21 and 22 which are in accordance with the requirements (**Table 2**). Meanwhile, the compounds that meet the requirements for distribution and excretion properties are compounds 1, 2, 4, 7, 8, 9, 11, 12, 13, 17, 18, and 19 (**Table 3**). Therefore, the compounds 9, 11, 13, 17 and 19 can be used as anti-inflammatory drug candidates that have good ADME. Prediction of the metabolism properties of these 22 compounds provides information about the possibility of these

compounds being metabolized in the liver. There are 2 compounds from 5 virtual screening compounds that are predicted to be metabolized in the liver. Compound 11 is a CYP3A4 substrate (M2) and a CYP1A2 inhibitor (M3), while compound 13 is a CYP3A4 substrate (M2) (**Table 4**). If the prediction results of this pharmacokinetic profile are related to previous research on predicting the affinity of compounds in *Hemigraphis alternata* leaves, it can be seen that 3,7,11,15-Tetramethyl-2-hexadecen-1-ol is a compound that has good activity and ADME for the inflammation treatment.

Table 2. The prediction results of absorption properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	A1	A2	A3	A4	A5	A6	A7
1	*15-Chloro-4-pentadecyne*	-7.634	1.402	92.577	-2.420	No	No	No
2	*4-(2-Methoxyphenyl)piperidine*	-1.835	1.385	91.872	-2.283	No	No	No
3	*Cyclobutanol*	0.092	1.463	98.450	-3.027	Yes	No	No
4	*1-Hexadecyne*	-7.801	1.382	92.797	-2.225	No	No	No
5	*2-Propylmalonic acid*	-1.323	0.667	74.589	-2.735	No	No	No
6	*n-Hexadecanoic acid*	-5.562	1.558	92.004	-2.717	No	No	No
7	*2-Hexylacrylonitrile*	-3.861	1.357	94.383	-1.278	No	No	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	-5.176	1.498	91.887	-1.477	No	No	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	-2.187	1.605	97.468	-2.814	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	-4.729	1.382	95.941	-1.606	No	No	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	-7.554	1.515	90.710	-2.576	No	No	Yes
12	*Z-2-Dodecenol*	-4.816	1.474	91.684	-1.529	No	No	No
13	*2-Methylenecholestan-3-ol*	-5.818	1.208	95.328	-2.733	No	No	Yes
14	*L-Alanine*	-2.887	0.466	81.091	-2.738	No	No	No
15	*levodopa*	-2.890	-0.289	47.741	-2.735	Yes	No	No
16	*Glycylsarcosine*	-2.699	0.545	68.130	-2.735	No	No	No
17	*5-Hydroxymethylfurfural*	-0.590	1.172	95.848	-3.416	No	No	No
18	*10-Undecyn-1-ol*	-3.892	1.476	93.273	-1.448	No	No	No
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	-0.757	1.621	97.700	-2.878	No	No	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	-2.799	0.903	92.210	-2.622	No	No	No

No	Compound	A1	A2	A3	A4	A5	A6	A7
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	-1.452	1.237	100	-3.221	No	No	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	-1.632	1.563	100	-3.097	No	No	No

Table 3. The prediction results of distribution and Excretion properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	D1	D2	D3	D4	E1	E2
1	*15-Chloro-4-pentadecyne*	0.534	0.062	0.917	-1.257	0.557	No
2	*4-(2-Methoxyphenyl)piperidine*	1.122	0.462	0.502	-2.260	0.880	No
3	*Cyclobutanol*	0.047	0.762	-0.031	-2.820	0.448	No
4	*1-Hexadecyne*	0.631	0.067	0.956	-1.364	1.870	No
5	*2-Propylmalonic acid*	-0.936	0.588	-0.060	-3.023	0.444	No
6	*n-Hexadecanoic acid*	-0.543	0.101	-0.111	-1.816	1.763	No
7	*2-Hexylacrylonitrile*	0.260	0.414	0.571	-1.976	0.550	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	0.370	0.234	0.652	-2.093	1.739	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	0.191	0.564	0.447	-2.813	1.266	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	0.531	0.271	0.609	-1.923	0.120	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	0.468	0	0.806	-1.563	1.686	No
12	*Z-2-Dodecenol*	0.358	0.275	0.713	-1.902	1.781	No
13	*2-Methylenecholestan-3-ol*	-0.145	0	0.808	-1.411	0.546	No
14	*L-Alanine*	-0.534	0.473	-0.412	-3.405	0.370	No
15	*levodopa*	-0.105	0.604	-0.843	-3.032	0.430	No
16	*Glycylsarcosine*	-0.680	0.538	-0.614	-3.183	0.217	No
17	*5-Hydroxymethylfurfural*	-0.146	0.744	-0.361	-2.914	0.614	No
18	*10-Undecyn-1-ol*	0.300	0.353	0.721	-1.957	1.713	No
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	-0.007	0.692	0.014	-2.842	0.569	No

No	Compound	D1	D2	D3	D4	E1	E2
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	0.209	0.207	-0.263	-2.106	0.537	No
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	0.015	0.617	-0.217	-2.909	0.198	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	0.558	0.678	-0.01	-3.357	0.135	No

Table 4. The prediction results of metabolism properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	M1	M2	M3	M4	M5	M6	M7
1	*15-Chloro-4-pentadecyne*	No	Yes	Yes	No	No	No	No
2	*4-(2-Methoxyphenyl)piperidine*	No	No	No	No	No	No	No
3	*Cyclobutanol*	No	No	No	No	No	No	No
4	*1-Hexadecyne*	No	Yes	Yes	No	No	No	No
5	*2-Propylmalonic acid*	No	No	No	No	No	No	No
6	*n-Hexadecanoic acid*	No	Yes	No	No	No	No	No
7	*2-Hexylacrylonitrile*	No	No	No	No	No	No	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	No	No	No	No	No	No	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	No	No	No	No	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	No	No	No	No	No	No	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	No	Yes	Yes	No	No	No	No
12	*Z-2-Dodecenol*	No	No	No	No	No	No	No
13	*2-Methylenecholestan-3-ol*	No	Yes	No	No	No	No	No
14	*L-Alanine*	No	No	No	No	No	No	No
15	*levodopa*	No	No	No	No	No	No	No
16	*Glycylsarcosine*	No	No	No	No	No	No	No
17	*5-Hydroxymethylfurfural*	No	No	No	No	No	No	No
18	*10-Undecyn-1-ol*	No	No	No	No	No	No	No

No	Compound	M1	M2	M3	M4	M5	M6	M7
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	No	No	No	No	No	No	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	No	No	Yes	No	No	No	No
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	No	No	No	No	No	No	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	No	No	No	No	No	No	No

CONCLUSION

There are 5 compounds predicted to have the best pharmacokinetic properties in *Hemigraphis alternata* leaves, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural* and *2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*. One of them which is predicted to have high affinity, good anti-inflammatory, absorption, distribution, metabolism and excretion is *3,7,11,15-Tetramethyl-2-hexadecen-1-ol*.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YY and RAR conducted the experiment, YY conducted the conceptualization, methodology, formal analysis, writing-review and editing, RAR conducted data curation and writing-original draft preparation.

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Section	Articles
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THE PREDICTION OF PHARMACOKINETIC PROPERTIES OF COMPOUNDS IN HEMIGRAPHIS ALTERNATA (BURM.F.) T. ANDER LEAVES USING PKCSM

ABSTRACT

The inflammatory process has a role in the healing process and leads the body's homeostasis normal. Untreated acute inflammation can lead to organ pathology leading to a chronic inflammatory phenotype. Prediction of the affinity of 22 compounds in *Hemigraphis alternata* leaves as anti-inflammatory has been conducted for COX-1, COX-2 and 5-LOX. The Prediction of pharmacokinetic properties of the compounds was carried out to obtain inflammatory drug candidates that have high affinity with adequate ADME. The application used in this research is pkCSM, a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. The pkCSM used 20 predictors which were divided into 4 properties, absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors) and excretion (2 predictors). Based on the prediction results, there are 5 compounds that have the best pharmacokinetic properties, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural and 2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*. *3,7,11,15-Tetramethyl-2-hexadecen-1-ol* is a compound that is predicted to have high affinity as an anti-inflammatory and good ADME.

Keywords: Pharmacokinetic, *Hemigraphis alternata*, pkCSM.

INTRODUCTION

Inflammation is a protective reaction of the immune system to defend the body from potentially harmful stimuli, both infectious and non-infectious agents that cause cell damage. It induces the inflammatory cells to be active and trigger inflammatory signaling pathways. The inflammatory process has an important function in the healing process so that abnormal body homeostasis can be restored. Acute inflammation that is not treated properly can cause organ pathology to worsen and eventually lead to a chronic inflammatory phenotype [1–3].

Hemigraphis alternata has various medicinal properties, including anti-inflammatory, anti-nociceptive and anti-diarrhoeal activities. Methanol and ethyl acetate extract of *Hemigraphis alternata* leaves has been shown to provide anti-inflammatory and non-toxic effects to mice [4]. There are 22 secondary metabolites that have been isolated in the leaves of this plant [5]. These compounds have predicted anti-inflammatory activity against COX-1, COX-2 and 5-LOX receptors. The compound predicted to have the highest affinity for COX-1 and COX-2 were *3,7,11,15-*

Tetramethyl-2-hexadecen-1-ol [6]. Meanwhile, the compound predicted to produce the highest affinity for 5-LOX was *n-Hexadecanoic acid* [7].

The relationship of pharmacokinetic properties, toxicity, and potency greatly affect the effectiveness of a drug. Determining the pharmacokinetic profile of a compound is carried out to determine the absorption, distribution, metabolism, and excretion (ADME) properties [8]. The initial assessment of ADME properties will help pharmaceutical researchers to select the best drug candidates for development and reject drug candidates that have a low probability of success. The aim of the in silico prediction of ADME properties is the accurate prediction of the in vivo pharmacokinetic properties of potential drug molecules in humans using only virtual structures [9]. The purpose of this study was to predict the pharmacokinetic properties (ADME) of 22 compounds contained in *Hemigraphis alternata* leaves through an in silico study.

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EXPERIMENTAL SECTION

Provide sufficient detail to allow the work to be reproduced, including Materials, Instrumentation, and procedures.

Materials

The SMILES format of 22 compounds contained in the leaves of *Hemigraphis alternata* was obtained from PubChem (pubchem.ncbi.nlm.nih.gov). Compounds that do not have the SMILES format in PubChem can be obtained by describing their structure in the Online SMILES Translator (https://cactus.nci.nih.gov).

Instrumentation

The prediction of pharmacokinetic properties of 22 compounds in the leaves of *Hemigraphis alternata* was conducted using pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction).

Procedure

pkCSM is based on general properties of compounds (molecular properties, toxicophores and pharmacophores) and distance-based graph signatures. In pkCSM there are 20 predictors that describe the pharmacokinetic properties of a compound. The predictors were divided into absorption of 7 predictors, distribution of 4 predictors, metabolism of 7 predictors and excretion of 2 predictors (**Table 1**) [8,10,11].

Table 1. Distribution of ADME predictors in pkCSM

Property	Predictor	Unit	Property	Predictor	Unit

Absorption	Water solubility (A1)	log mol/L	Distribution	CNS permeability (D4)	log PS
Absorption	Caco2 permeability (A2)	log Papp in 10-6 cm/s	Metabolism	CYP2D6 substrate (M1)	Yes/No
Absorption	Intestinal absorption (human) (A3)	% Absorbed	Metabolism	CYP3A4 substrate (M2)	Yes/No
Absorption	Skin Permeability (A4)	log Kp	Metabolism	CYP1A2 inhibitor (M3)	Yes/No
Absorption	P-glycoprotein substrate (A5)	Yes/No	Metabolism	CYP2C19 inhibitor (M4)	Yes/No
Absorption	P-glycoprotein I inhibitor (A6)	Yes/No	Metabolism	CYP2C9 inhibitor (M5)	Yes/No
Absorption	P-glycoprotein II inhibitor (A7)	Yes/No	Metabolism	CYP2D6 inhibitor (M6)	Yes/No
Distribution	VDss (human) (D1)	log L/kg	Metabolism	CYP3A4 inhibitor (M7)	Yes/No
Distribution	Fraction unbound (human) (D2)	Fu	Excretion	Total Clearance (E1)	log ml/min/kg
Distribution	BBB permeability (D3)	log BB	Excretion	Renal OCT2 substrate (E2)	Yes/No

In this study, virtual screening was carried out to obtain several compounds that had good ADME. Virtual screening is based on the results of the ADME predictor which has a numerical value with certain limitations. The predictors were Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3), CNS permeability (D4), total clearance (E1) [12]. The requirements are log Papp in 10-6 cm/s in Caco2 permeability (A2) >

0.9, intestinal absorption (human) (A3) > 30%, log Kp ≥ -2.5 in skin permeability (A4), log L/kg ≥ -0.15 in VDss (human) (D1), log BB ≥ -1 in BBB permeability (D3), log PS ≥ -3 in CNS permeability (D4).

The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54, 5 compounds with the best ADME were obtained. Subsequently, these results were compared with the predicted affinity in previous studies and 1 compound with good affinity and ADME was obtained [8].

RESULTS AND DISCUSSION

pkCSM is a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. pkCSM adapts the Cutoff Scanning concept to represent molecular and chemical structures to represent and predict their pharmacokinetic properties [8].

Water solubility is an important factor for a drug to show a better pharmacological response for oral administration. Drugs that have good water solubility properties will cause the drug to have good absorption and bioavailability properties. Good drug absorption and bioavailability can increase the plasma drug concentration at the target site to perform therapeutic functions [13].

Caco-2 cells are a cell line derived from colorectal adenocarcinoma [14]. The Caco-2 model was used to predict the possible gastrointestinal permeability of drugs in pre-clinical trials. This model expresses cytochrome P450 enzymes, transporters, microvilli, and enterocytes based on characteristics identical to those of the human small intestine [15]. The permeability of Caco-2 of a compound is high if it has a Papp > 8 x 10-6 cm/s. The permeability of Caco-2 is high if the predictive value is > 0.90 in the pkCSM predictive model [8].

The intestine is the main site for absorption of oral drugs. The compound is predicted to have low Intestinal absorption (human) if the value is < 30% [8]. The skin is the boundary between the internal and external body environment. Skin characteristics and properties can modify and affect drug delivery and toxicity [16]. A compound has a tendency to be skin permeable which is expressed by the skin permeability constant logKp (cm/hour). The logKp value of the compound > -2.5 indicates that the compound has low skin permeability [8].

Substrate P-glycoprotein is an ATP-binding cassette (ABC) transporter that functions as a biological barrier by removing toxins and xenobiotics from cells. P-glycoprotein I/II inhibitor is the ability of the compound to inhibit the transport of P-glycoprotein I and P-glycoprotein II. P-glycoprotein-mediated modulation of transport has significant pharmacokinetic implications for Pgp substrates. Inhibition of P-glycoprotein I or P-glycoprotein II can be exploited for certain therapeutic advantages or produce contraindications [8].

VDss (human) is the total amount of drug in the body divided by the total concentration of drug in plasma at steady state. This condition occurs when the system undergoes an infusion of the

drug at a constant rate into the plasma and all drug concentrations in the body do not change [17]. VDss is low if the value is < 0.71 L/kg (log VDss < -0.15) and high if the value is > 2.81 L/kg (log VDss > 0.45). The effectiveness of a drug can be affected by the ability of the drug for binding proteins in the blood. The larger the fraction of the drug that is not bound to protein (fraction unbound), the more efficiently the drug will cross the cell membrane or diffuse [8].

Increased permeability of the BBB (Blood-Brain Barrier) which is a physical and biochemical barrier that plays a role in the defense of cerebral homeostasis can affect the pathological development of ischemic tissue [18,19]. A compound with a logBB > 0.3 can easily pass through BBB and a compound with a logBB < 1 is not well distributed to the brain. The ability of drug compounds to penetrate the CNS (Central Nervous System) can be determined from the value of the blood-brain permeability surface area product (logPS). This value was obtained from in situ brain perfusion with the compound directly injected into the carotid artery without any systemic distribution effect that could distort brain penetration. Compounds with logPS > -2 could penetrate the CNS, while compounds with logPS < -3 could not penetrate the CNS [8].

Cytochrome P450 is a detoxifying enzyme that can be found in the liver. Cytochrome P450 generally plays a role in drug metabolism. However, P450 inhibitors can dramatically alter drug pharmacokinetics. Therefore, it is important to know whether the given compound is a CYP2D6/CYP3A4 substrate predicted to be metabolized by P450. Cytochrome P450 oxidizes xenobiotics to be finally excreted. Many drugs are inactivated by cytochrome P450 and some can be activated by it. These enzyme inhibitors can affect drug metabolism and are contraindicated. It is therefore important to assess the ability of the compound to inhibit cytochrome P450 (isoform CYP1A2/CYP2C19/CYP2C9/CYP2D6/CYP3A4). A compound is considered a cytochrome P450 inhibitor if the concentration required to cause 50% inhibition is < 10 M [8].

Drug clearance is the volume of plasma in the vascular compartment that is cleared of drug per unit time. Total clearance is the sum of all body clearances. Total clearance gives an indication of drug elimination from the central compartment without reference to the mechanism of the process [20]. Organic Cation Transporter 2 (OCT2) is a renal uptake transporter that has an important role in the disposition and renal clearance of drugs or endogenous compounds. OCT2 substrates may cause adverse effects when administered concomitantly with OCT2 inhibitors [8].

In the results of the prediction of adsorption properties obtained compounds 3, 6, 9, 11, 13, 17, 19, 20, 21 and 22 which are in accordance with the requirements (**Table 2**). Meanwhile, the compounds that meet the requirements for distribution and excretion properties are compounds 1, 2, 4, 7, 8, 9, 11, 12, 13, 17, 18, and 19 (**Table 3**). Therefore, the compounds 9, 11, 13, 17 and 19 can be used as anti-inflammatory drug candidates that have good ADME. Prediction of the metabolism properties of these 22 compounds provides information about the possibility of these compounds being metabolized in the liver. There are 2 compounds from 5 virtual screening compounds that are predicted to be metabolized in the liver. Compound 11 is a CYP3A4 substrate

(M2) and a CYP1A2 inhibitor (M3), while compound 13 is a CYP3A4 substrate (M2) (**Table 4**). If the prediction results of this pharmacokinetic profile are related to previous research on predicting the affinity of compounds in *Hemigraphis alternata* leaves, it can be seen that 3,7,11,15-Tetramethyl-2-hexadecen-1-ol is a compound that has good activity and ADME for the inflammation treatment.

Table 2. The prediction results of absorption properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	A1	A2	A3	A4	A5	A6	A7
1	*15-Chloro-4-pentadecyne*	-7.634	1.402	92.577	-2.420	No	No	No
2	*4-(2-Methoxyphenyl)piperidine*	-1.835	1.385	91.872	-2.283	No	No	No
3	*Cyclobutanol*	0.092	1.463	98.450	-3.027	Yes	No	No
4	*1-Hexadecyne*	-7.801	1.382	92.797	-2.225	No	No	No
5	*2-Propylmalonic acid*	-1.323	0.667	74.589	-2.735	No	No	No
6	*n-Hexadecanoic acid*	-5.562	1.558	92.004	-2.717	No	No	No
7	*2-Hexylacrylonitrile*	-3.861	1.357	94.383	-1.278	No	No	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	-5.176	1.498	91.887	-1.477	No	No	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	-2.187	1.605	97.468	-2.814	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	-4.729	1.382	95.941	-1.606	No	No	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	-7.554	1.515	90.710	-2.576	No	No	Yes
12	*Z-2-Dodecenol*	-4.816	1.474	91.684	-1.529	No	No	No
13	*2-Methylenecholestan-3-ol*	-5.818	1.208	95.328	-2.733	No	No	Yes
14	*L-Alanine*	-2.887	0.466	81.091	-2.738	No	No	No
15	*levodopa*	-2.890	-0.289	47.741	-2.735	Yes	No	No
16	*Glycylsarcosine*	-2.699	0.545	68.130	-2.735	No	No	No
17	*5-Hydroxymethylfurfural*	-0.590	1.172	95.848	-3.416	No	No	No
18	*10-Undecyn-1-ol*	-3.892	1.476	93.273	-1.448	No	No	No
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	-0.757	1.621	97.700	-2.878	No	No	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	-2.799	0.903	92.210	-2.622	No	No	No

No	Compound	A1	A2	A3	A4	A5	A6	A7
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	-1.452	1.237	100	-3.221	No	No	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	-1.632	1.563	100	-3.097	No	No	No

Table 3. The prediction results of distribution and Excretion properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	D1	D2	D3	D4	E1	E2
1	*15-Chloro-4-pentadecyne*	0.534	0.062	0.917	-1.257	0.557	No
2	*4-(2-Methoxyphenyl)piperidine*	1.122	0.462	0.502	-2.260	0.880	No
3	*Cyclobutanol*	0.047	0.762	-0.031	-2.820	0.448	No
4	*1-Hexadecyne*	0.631	0.067	0.956	-1.364	1.870	No
5	*2-Propylmalonic acid*	-0.936	0.588	-0.060	-3.023	0.444	No
6	*n-Hexadecanoic acid*	-0.543	0.101	-0.111	-1.816	1.763	No
7	*2-Hexylacrylonitrile*	0.260	0.414	0.571	-1.976	0.550	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	0.370	0.234	0.652	-2.093	1.739	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	0.191	0.564	0.447	-2.813	1.266	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	0.531	0.271	0.609	-1.923	0.120	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	0.468	0	0.806	-1.563	1.686	No
12	*Z-2-Dodecenol*	0.358	0.275	0.713	-1.902	1.781	No
13	*2-Methylenecholestan-3-ol*	-0.145	0	0.808	-1.411	0.546	No
14	*L-Alanine*	-0.534	0.473	-0.412	-3.405	0.370	No
15	*levodopa*	-0.105	0.604	-0.843	-3.032	0.430	No
16	*Glycylsarcosine*	-0.680	0.538	-0.614	-3.183	0.217	No
17	*5-Hydroxymethylfurfural*	-0.146	0.744	-0.361	-2.914	0.614	No
18	*10-Undecyn-1-ol*	0.300	0.353	0.721	-1.957	1.713	No
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	-0.007	0.692	0.014	-2.842	0.569	No

No	Compound	D1	D2	D3	D4	E1	E2
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	0.209	0.207	-0.263	-2.106	0.537	No
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	0.015	0.617	-0.217	-2.909	0.198	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	0.558	0.678	-0.01	-3.357	0.135	No

Table 4. The prediction results of metabolism properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	M1	M2	M3	M4	M5	M6	M7
1	*15-Chloro-4-pentadecyne*	No	Yes	Yes	No	No	No	No
2	*4-(2-Methoxyphenyl)piperidine*	No	No	No	No	No	No	No
3	*Cyclobutanol*	No	No	No	No	No	No	No
4	*1-Hexadecyne*	No	Yes	Yes	No	No	No	No
5	*2-Propylmalonic acid*	No	No	No	No	No	No	No
6	*n-Hexadecanoic acid*	No	Yes	No	No	No	No	No
7	*2-Hexylacrylonitrile*	No	No	No	No	No	No	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	No	No	No	No	No	No	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	No	No	No	No	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	No	No	No	No	No	No	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	No	Yes	Yes	No	No	No	No
12	*Z-2-Dodecenol*	No	No	No	No	No	No	No
13	*2-Methylenecholestan-3-ol*	No	Yes	No	No	No	No	No
14	*L-Alanine*	No	No	No	No	No	No	No
15	*levodopa*	No	No	No	No	No	No	No
16	*Glycylsarcosine*	No	No	No	No	No	No	No
17	*5-Hydroxymethylfurfural*	No	No	No	No	No	No	No
18	*10-Undecyn-1-ol*	No	No	No	No	No	No	No

No	Compound	M1	M2	M3	M4	M5	M6	M7
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	No	No	No	No	No	No	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	No	No	Yes	No	No	No	No
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	No	No	No	No	No	No	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	No	No	No	No	No	No	No

CONCLUSION

There are 5 compounds predicted to have the best pharmacokinetic properties in *Hemigraphis alternata* leaves, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural* and *2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*. One of them which is predicted to have high affinity, good anti-inflammatory, absorption, distribution, metabolism and excretion is *3,7,11,15-Tetramethyl-2-hexadecen-1-ol*.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YY and RAR conducted the experiment, YY conducted the conceptualization, methodology, formal analysis, writing-review and editing, RAR conducted data curation and writing-original draft preparation.

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Review Comments to the article number 73117-246939-2
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Reviewer Comments

This article is interesting and written using up to date references but there are some writings that need to be improved according to the specific comments below.

1. There are some writing errors, such as capitalization not at the beginning of the sentence (for example in fourth sentence abstract), writing abbreviations that have not been preceded by their abbreviations (for examples COX, LOX, ADME, pkCSM in the abstract).
2. This study combines several previous studies. However, in the abstract, it is not clear which one was done by other researchers or what was done by the author of this article. For example, as many as 22 secondary metabolites analyzed for their pharmacokinetic profiles using pkCSM in this article are the result of other people's research. Authors may have conducted previous in silico research to see the predictions of these 22 metabolites as anti-inflammatory (but the in silico docking method used and the results of the in silico research did not explain yet). Furthermore, this study actually only determined pharmacokinetic using pkCSM, but this article also wrote conclusions about compounds that have potential as anti-inflammatory (which were not carried out) and also their good pharmacokinetic parameter. As a suggestion, it is better to make a good common thread regarding the research that has been done previously, the results that have been achieved, and its relationship with the research conducted in this article.
3. Try using MESH on demand to search for keywords. For the word pharmacokinetic it is recommended to change it to pharmacokinetic parameters/profiles.
4. pkCSM was used as a tool to measure the pharmacokinetic parameters of the secondary metabolite *Hemigraphis alternata*. Therefore, it is necessary to add in the background section about the pkCSM method (their weaknesses/strengths, and add information on the existence of studies showing a positive correlation of the results of pkCSM with the results of in vivo pharmacokinetic studies).
5. In addition to the data for compounds whose pharmacokinetic profile will be determined, the structure of secondary metabolites of *Hemigraphis alternata* can be drawn in 3D using Chem bio Draw (accompanied by molecular weight information).
6. Table 1 can be made more comprehensive so that it is easier to understand. You can add a column description of the predicted value for each parameter (for example, the

requirements for a good intestinal absorption value > 30/80% and each value can be referenced).

For example:

Pharmacokinetic Parameter	Predictor (Code)	Unit	Requirement value as good pharmacokinetic parameter	References
Absorption	Water solubility			

Distribution	---			
	and further			

7. Tables 2, 3 and 4 still have to be given a notes/descriptions under each table (information about the predictor code being analyzed) for example D1 = ..., D2 = ... in order to make it easier to read the stand-alone table. In column 2, the name of the compound can be given the molecular weight information.
8. The predictor values for each pharmacokinetic parameter have been written in table 1, there is no need to discuss it again in the results and discussion section. It is better to discuss how to select compounds (out of a total of 22 compounds) for each parameters (absorption/distribution/metabolism/excretion) based on the results in table 2-4. For example, a compound is selected if it satisfies all of the criteria for predictor values A1-A7 (absorption parameters), or uses only few important predictor categories.
9. This article need to increase the number of references used

3

Bukti konfirmasi submit revisi pertama, respon kepada reviewer, dan artikel yang diresubmit

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#73117 Review

SUMMARY REVIEW EDITING

Submission

Authors	Yeni Yeni, Rizky Arcinthya Rachmania
Title	The Prediction of Pharmacokinetic Properties of Compounds in *Hemigraphis alternata* (Burm.F.) T. Ander Leaves Using pkCSM
Section	Articles
Editor	Stalis Ethica

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No.	The Reviewer's Comments	Author's Revision
1.	Describe the insilico generally?	The development of new drug candidates is a complex process that is expensive and takes a long time. Computer-aided drug design (CADD) or in silico computational models have an important role in the discovery of new drugs. Its application shortens the research time and resources required for the rational design of new drug candidates. The developments in the pharmaceutical field have increased the demand for the development of more reliable techniques to predict the pharmacokinetic properties of new drug candidates. At the present, the computational prediction tools have been widely used in the drug discovery process due to the advancement of computational algorithms and large knowledge databases. In addition, the in silico methods have been carried out in several drug discoveries currently used for the treatment of diseases
2.	Please describe why 5 compound have best pharmacokinetic in discussion	Therefore, the compounds 9 (*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*), 11 (*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*), 13 (*2-Methylene cholestan-3-ol*), 17 (*5-Hydroxymethylfurfural*) and 19 (*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*) can be used as anti-inflammatory drug candidates that have good ADME because these compounds are intersection which meet the requirements of absorption, distribution and excretion predictors.
3.	There are some writing errors, such as capitalization not at the beginning of the sentence (for example in fourth sentence abstract), writing abbreviations that have not been preceded by their abbreviations (for examples COX, LOX, ADME, pkCSM in the abstract).	We changed the words COX, LOX, ADME in abstract. There is not definite abbreviation for pkCSM tool, so that we define it in the abstract.
4.	This study combines several previous studies. However, in the abstract, it is not clear which one was done by other researchers or what was done by the author of this article. For example, as many as 22 secondary metabolites analyzed for their pharmacokinetic profiles using pkCSM in this	*Hemigraphis alternata* is a plant that has anti-inflammatory activity. The compounds contained in *Hemigraphis alternata* leaves have been predicted to have affinity for receptors that play

	article are the result of other people's research. Authors may have conducted previous in silico research to see the predictions of these 22 metabolites as anti-inflammatory (but the in silico docking method used and the results of the in silico research did not explain yet). Furthermore, this study actually only determined pharmacokinetic using pkCSM, but this article also wrote conclusions about compounds that have potential as anti-inflammatory (which were not carried out) and also their good pharmacokinetic parameter. As a suggestion, it is better to make a good common thread regarding the research that has been done previously, the results that have been achieved, and its relationship with the research conducted in this article.	a role in the inflammatory process. A large number of drug candidates were withdrawn from preclinical trials due to their poor pharmacokinetic profiles. Drug compounds must cross the barriers that exist in the body to reach their biological targets so that they can have an effect. The Prediction of pharmacokinetic properties of 22 compounds in *Hemigraphis alternata* leaves was carried out to obtain inflammatory drug candidates that have adequate pharmacokinetic profiles. The application used in this research is pkCSM, a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. The pkCSM used 20 predictors which were divided into 4 properties, absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors) and excretion (2 predictors). Based on the prediction results, there are 5 compounds that have the best pharmacokinetic properties, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural and 2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*.
5.	Try using MESH on demand to search for keywords. For the word pharmacokinetic it is	**Keywords:** *Hemigraphis alternata*, Pharmacokinetic profiles, pkCSM.

	recommended to change it to pharmacokinetic parameters/profiles.	
6.	pkCSM was used as a tool to measure the pharmacokinetic parameters of the secondary metabolite Hemigraphis alternata. Therefore, it is necessary to add in the background section about the pkCSM method (their weaknesses/strengths, and add information on the existence of studies showing a positive correlation of the results of pkCSM with the results of in vivo pharmacokinetic studies).	pkCSM is a tool that can characterize the pharmacokinetic profile of compounds comprehensively. The concept used to predict the predictors by this tool is graph-based structural signatures which train the prediction algorithm by encoding the pattern of distances between atoms. Graphical modeling is the result of an intuitive and well-established mathematical representation of chemical entities. In pkCSM, different predictors including molecular structure and chemistry can be extracted [14–16]. Despite the distribution of experimental values and variability in the size of the data set, pkCSM model was able to achieve a good correlation with experimental results through regression analysis of the ADME predictors [8].
7.	In addition to the data for compounds whose pharmacokinetic profile will be determined, the structure of secondary metabolites of Hemigraphis alternata can be drawn in 3D using Chem bio Draw (accompanied by molecular weight information).	We do not put the 3D structure of the compounds but 2D structure and molecular weight information because it considers the need to know the atoms that make up the compounds. See Figure 1.
8.	Table 1 can be made more comprehensive so that it is easier to understand. You can add a column description of the predicted value for each parameter (for example, the requirements for a good intestinal absorption value > 30/80% and each value can be referenced).	Already fixed. See Table 1.
9.	Tables 2, 3 and 4 still have to be given a notes/descriptions under each table (information about the predictor code being analyzed) for example D1 = ..., D2 = ... in order to make it easier to read the stand-alone table. In column 2, the name of the compound can be given the molecular weight information.	Already fixed See Table 2, 3 and 4.
10.	The predictor values for each pharmacokinetic parameter have been written in table 1, there is no need to discuss it again in the results and discussion section. It is better to discuss how to select compounds (out of a total of 22 compounds) for each parameters (absorption/distribution/metabolism/excretion)	We have deleted the predictor values in discusion and give more information how to analyze the result of pharmacikinetic properties prediction.

	based on the results in table 2-4. For example, a compound is selected if it satisfies all of the criteria for predictor values A1-A7 (absorption parameters), or uses only few important predictor categories.	In this study, the screening process was based on predictors which had a limit value to determine whether or not the pharmacokinetic profile of a compound was good. The predictors included Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3) and CNS permeability (D4). The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54.
11.	This article need to increase the number of references used	We added 7 references related to this research [10] Brogi, S., Ramalho, T.C., Kuca, K., Medina-Franco, J.L. and Valko, M., 2020, In silico methods for drug design and discovery, *Front. Chem*., 8, 612–616. [11] Chandrasekaran, B., Abed, S.N., Al-Attraqchi, O., Kuche, K. and Tekade, R.K., 2018, Computer-aided prediction of pharmacokinetic (ADMET) properties, in dosage form design parameters, pp. 731-755, Academic Press. [12] Shaker, B., Ahmad, S., Lee, J., Jung, C. and Na, D., 2021, In silico methods and tools for drug discovery, *Comput. Biol. Med., 137*, 104851–104865.

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[15] Pires, D.E., Kaminskas, L.M. and Ascher, D.B., 2018, Prediction and optimization of pharmacokinetic and toxicity properties of the ligand, in computational drug discovery and design, pp. 271–284, Humana Press.

[16] Udrea, A. M., Gradisteanu Pircalabioru, G., Boboc, A. A., Mares, C., Dinache, A., Mernea, M., and Avram, S., 2021, Advanced bioinformatics tools in the pharmacokinetic profiles of natural and synthetic compounds with anti-diabetic activity, *Biomolecules*, 11 (11), 1692–1722.

THE PREDICTION OF PHARMACOKINETIC PROPERTIES OF COMPOUNDS IN HEMIGRAPHIS ALTERNATA (BURM.F.) T. ANDER LEAVES USING PKCSM

Yeni Yeni1[1,]*, and Rizky Arcinthya Rachmania[1]

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ABSTRACT

The inflammatory process has a role in the healing process and leads the body's homeostasis normal. Untreated acute inflammation can lead to organ pathology leading to a chronic inflammatory phenotype. *Hemigraphis alternata* is a plant that has anti-inflammatory activity. The compounds contained in *Hemigraphis alternata* leaves have been predicted to have affinity for receptors that play a role in the inflammatory process. A large number of drug candidates were withdrawn from preclinical trials due to their poor pharmacokinetic profiles. Drug compounds must cross the barriers that exist in the body to reach their biological targets so that they can have an effect. The Prediction of pharmacokinetic properties of 22 compounds in *Hemigraphis alternata* leaves was carried out to obtain inflammatory drug candidates that have adequate pharmacokinetic profiles. The application used in this research is pkCSM, a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. The pkCSM used 20 predictors which were divided into 4 properties, absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors) and excretion (2 predictors). Based on the prediction results, there are 5 compounds that have the best pharmacokinetic properties, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural and 2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*.

Keywords: *Hemigraphis alternata*, Pharmacokinetic profiles, pkCSM.

INTRODUCTION

Inflammation is a protective reaction of the immune system to defend the body from potentially harmful stimuli, both infectious and non-infectious agents that cause cell damage. It induces the inflammatory cells to be active and trigger inflammatory signaling pathways. The inflammatory process has an important function in the healing process so that abnormal body homeostasis can be restored. Acute inflammation that is not treated properly can cause organ pathology to worsen and eventually lead to a chronic inflammatory phenotype [1–3].

Hemigraphis alternata has various medicinal properties, including anti-inflammatory, anti-nociceptive and anti-diarrhoeal activities. Methanol and ethyl acetate extract of *Hemigraphis alternata* leaves has been shown to provide anti-inflammatory and non-toxic effects to mice [4]. There are 22 secondary metabolites that have been isolated in the leaves of this plant (**Figure 1**) [5]. These compounds have predicted anti-inflammatory activity against COX-1 and 5-LOX receptors [6,7].

The relationship of pharmacokinetic properties, toxicity, and potency greatly affect the effectiveness of a drug. Determining the pharmacokinetic profiles of a compound is carried out to determine the absorption, distribution, metabolism, and excretion (ADME) properties [8]. The initial assessment of ADME properties will help pharmaceutical researchers to select the best drug candidates for development and reject drug candidates that have a low probability of success [9]. The development of new drug candidates is a complex process that is expensive and takes a long time. Computer-aided drug design (CADD) or in silico computational models have an important role in the discovery of new drugs. Its application shortens the research time and resources required for the rational design of new drug candidates. The developments in the pharmaceutical field have increased the demand for the development of more reliable techniques to predict the pharmacokinetic properties of new drug candidates. At the present, the computational prediction tools have been widely used in the drug discovery process due to the advancement of computational algorithms and large knowledge databases. In addition, the in silico methods have been carried out in several drug discoveries currently used for the treatment of diseases [10–13].

pkCSM is a tool that can characterize the pharmacokinetic profile of compounds comprehensively. The concept used to predict the predictors by this tool is graph-based structural signatures which train the prediction algorithm by encoding the pattern of distances between atoms. Graphical modeling is the result of an intuitive and well-established mathematical representation of chemical entities. In pkCSM, different predictors including molecular structure and chemistry can be extracted [14–16]. Despite the distribution of experimental values and variability in the size of the data set, pkCSM model was able to achieve a good correlation with experimental results through regression analysis of the ADME predictors [8]. The aim of the in silico prediction of ADME properties is the accurate prediction of the in vivo pharmacokinetic properties of potential drug molecules in humans using only virtual structures The purpose of this study was to predict the pharmacokinetic properties (ADME) of 22 compounds contained in *Hemigraphis alternata* leaves through an in silico study.

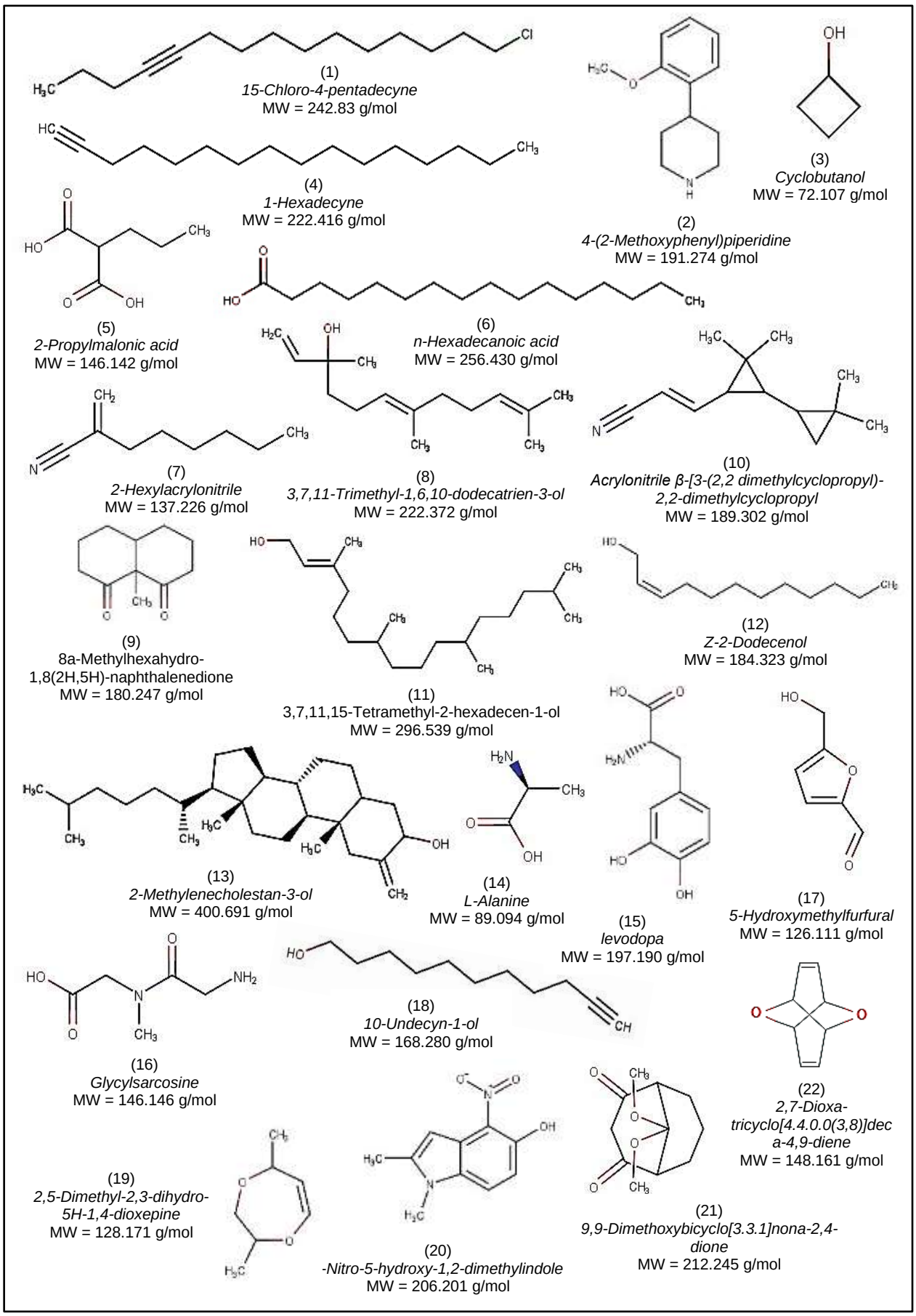

Figure 1. The compounds contained in *Hemigraphis alternata* leaves.

EXPERIMENTAL SECTION

Provide sufficient detail to allow the work to be reproduced, including Materials, Instrumentation, and procedures.

Materials

The SMILES format of 22 compounds contained in the leaves of *Hemigraphis alternata* was obtained from PubChem (pubchem.ncbi.nlm.nih.gov). Compounds that do not have the SMILES format in PubChem can be obtained by describing their structure in the Online SMILES Translator (https://cactus.nci.nih.gov).

Instrumentation

The prediction of pharmacokinetic properties of 22 compounds in the leaves of *Hemigraphis alternata* was conducted using pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction).

Procedure

pkCSM is based on general properties of compounds (molecular properties, toxicophores and pharmacophores) and distance-based graph signatures. In pkCSM there are 20 predictors that describe the pharmacokinetic properties of a compound. The predictors were divided into absorption of 7 predictors, distribution of 4 predictors, metabolism of 7 predictors and excretion of 2 predictors (**Table 1**) [8,17,18].

Table 1. Distribution of ADME predictors in pkCSM

Pharmacokinetic Parameter	Predictor (Code)	Unit	Requirement value	References
Absorption	Water solubility (A1)	log mol/L	-	[8]
	Caco2 permeability (A2)	log Papp in 10^{-6} cm/s	> 0.9	[8]
	Intestinal absorption (human) (A3)	% Absorbed	> 30%	[8]
	Skin Permeability (A4)	log Kp	≥ -2.5	[8]
	P-glycoprotein substrate (A5)	Yes/No	-	[8]
	P-glycoprotein I inhibitor (A6)	Yes/No	-	[8]

Pharmacokinetic Parameter	Predictor (Code)	Unit	Requirement value	References
	P-glycoprotein II inhibitor (A7)	Yes/No	-	[8]
Distribution	VDss (human) (D1)	log L/kg	≥ -0.15	[8]
	Fraction unbound (human) (D2)	Fu	-	[8]
	BBB permeability (D3)	log BB	≥ -1	[8]
	CNS permeability (D4)	log PS	≥ -3	[8]
Metabolism	CYP2D6 substrate (M1)	Yes/No	-	[8]
	CYP3A4 substrate (M2)	Yes/No	-	[8]
	CYP1A2 inhibitor (M3)	Yes/No	-	[8]
	CYP2C19 inhibitor (M4)	Yes/No	-	[8]
	CYP2C9 inhibitor (M5)	Yes/No	-	[8]
	CYP2D6 inhibitor (M6)	Yes/No	-	[8]
	CYP3A4 inhibitor (M7)	Yes/No	-	[8]
Excretion	Total Clearance (E1)	log ml/min/kg	Higher is better	[8]
	Renal OCT2 substrate (E2)	Yes/No	-	[8]

In this study, virtual screening was carried out to obtain several compounds that had good ADME. Virtual screening is based on the results of the ADME predictor which has a numerical value with certain limitations. The predictors were Caco2 permeability (A2), intestinal absorption (human)

(A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3), CNS permeability (D4) and total clearance (E1) [19].

Initially, test compounds were selected based on predictors of Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3) and CNS permeability (D4). The compounds that meet the requirements will be re-screened based on the highest total clearance (E1) value [8].

RESULTS AND DISCUSSION

pkCSM is a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. pkCSM adapts the Cutoff Scanning concept to represent molecular and chemical structures to represent and predict their pharmacokinetic properties [8].

Water solubility is an important factor for a drug to show a better pharmacological response for oral administration. Drugs that have good water solubility properties will cause the drug to have good absorption and bioavailability properties. Good drug absorption and bioavailability can increase the plasma drug concentration at the target site to perform therapeutic functions [20].

Caco-2 cells are a cell line derived from colorectal adenocarcinoma [21]. The Caco-2 model was used to predict the possible gastrointestinal permeability of drugs in pre-clinical trials. This model expresses cytochrome P450 enzymes, transporters, microvilli, and enterocytes based on characteristics identical to those of the human small intestine [22]. The permeability of Caco-2 of a compound is high if it has a Papp > 8 x 10^{-6} cm/s.

The intestine is the main site for absorption of oral drugs. The skin is the boundary between the internal and external body environment. Skin characteristics and properties can modify and affect drug delivery and toxicity [23]. A compound has a tendency to be skin permeable which is expressed by the skin permeability constant logKp (cm/hour).

Substrate P-glycoprotein is an ATP-binding cassette (ABC) transporter that functions as a biological barrier by removing toxins and xenobiotics from cells. P-glycoprotein I/II inhibitor is the ability of the compound to inhibit the transport of P-glycoprotein I and P-glycoprotein II. P-glycoprotein-mediated modulation of transport has significant pharmacokinetic implications for Pgp substrates. Inhibition of P-glycoprotein I or P-glycoprotein II can be exploited for certain therapeutic advantages or produce contraindications [8].

VDss (human) is the total amount of drug in the body divided by the total concentration of drug in plasma at steady state. This condition occurs when the system undergoes an infusion of the drug at a constant rate into the plasma and all drug concentrations in the body do not change [24]. The effectiveness of a drug can be affected by the ability of the drug for binding proteins in the blood. The larger the fraction of the drug that is not bound to protein (fraction unbound), the more efficiently the drug will cross the cell membrane or diffuse [8].

Increased permeability of the BBB (Blood-Brain Barrier) which is a physical and biochemical barrier that plays a role in the defense of cerebral homeostasis can affect the pathological development of ischemic tissue [25,26]. The ability of drug compounds to penetrate the CNS (Central Nervous System) can be determined from the value of the blood-brain permeability surface area product (logPS). This value was obtained from in situ brain perfusion with the compound directly injected into the carotid artery without any systemic distribution effect that could distort brain penetration [8].

Cytochrome P450 is a detoxifying enzyme that can be found in the liver. Cytochrome P450 generally plays a role in drug metabolism. However, P450 inhibitors can dramatically alter drug pharmacokinetics. Therefore, it is important to know whether the given compound is a CYP2D6/CYP3A4 substrate predicted to be metabolized by P450. Cytochrome P450 oxidizes xenobiotics to be finally excreted. Many drugs are inactivated by cytochrome P450 and some can be activated by it. These enzyme inhibitors can affect drug metabolism and are contraindicated. It is therefore important to assess the ability of the compound to inhibit cytochrome P450 (isoform CYP1A2/CYP2C19/CYP2C9/CYP2D6/CYP3A4). A compound is considered a cytochrome P450 inhibitor if the concentration required to cause 50% inhibition is < 10 M [8].

Drug clearance is the volume of plasma in the vascular compartment that is cleared of drug per unit time. Total clearance is the sum of all body clearances. Total clearance gives an indication of drug elimination from the central compartment without reference to the mechanism of the process [27]. Organic Cation Transporter 2 (OCT2) is a renal uptake transporter that has an important role in the disposition and renal clearance of drugs or endogenous compounds. OCT2 substrates may cause adverse effects when administered concomitantly with OCT2 inhibitors [8].

In the results of the prediction of absorption properties obtained compounds 3, 6, 9, 11, 13, 17, 19, 20, 21 and 22 which are in accordance with the requirements (**Table 2**). Meanwhile, the compounds that meet the requirements for distribution and excretion properties are compounds 1, 2, 4, 7, 8, 9, 11, 12, 13, 17, 18, and 19 (**Table 3**). Therefore, the compounds 9 (*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*), 11 (*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*), 13 (*2-Methylene cholestan-3-ol*), 17 (*5-Hydroxymethylfurfural*) and 19 (*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*) can be used as anti-inflammatory drug candidates that have good ADME because these compounds are intersection which meet the requirements of absorption, distribution and excretion predictors. Prediction of the metabolism properties of these 22 compounds provides information about the possibility of these compounds being metabolized in the liver. There are 2 compounds from 5 virtual screening compounds that are predicted to be metabolized in the liver. Compound 11 is a CYP3A4 substrate (M2) and a CYP1A2 inhibitor (M3), while compound 13 is a CYP3A4 substrate (M2) (**Table 4**). In this study, the screening process was based on predictors which had a limit value to determine whether or not the pharmacokinetic profile of a compound was good. The predictors included Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1),

BBB permeability (D3) and CNS permeability (D4). The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54.

Table 2. The prediction results of absorption properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	MW	A1	A2	A3	A4	A5	A6	A7
1	*15-Chloro-4-pentadecyne*	242.830	-7.634	1.402	92.577	-2.420	No	No	No
2	*4-(2-Methoxyphenyl)piperidine*	191.274	-1.835	1.385	91.872	-2.283	No	No	No
3	*Cyclobutanol*	72.107	0.092	1.463	98.450	-3.027	Yes	No	No
4	*1-Hexadecyne*	222.416	-7.801	1.382	92.797	-2.225	No	No	No
5	*2-Propylmalonic acid*	146.142	-1.323	0.667	74.589	-2.735	No	No	No
6	*n-Hexadecanoic acid*	256.430	-5.562	1.558	92.004	-2.717	No	No	No
7	*2-Hexylacrylonitrile*	137.226	-3.861	1.357	94.383	-1.278	No	No	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	222.372	-5.176	1.498	91.887	-1.477	No	No	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	180.247	-2.187	1.605	97.468	-2.814	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	189.302	-4.729	1.382	95.941	-1.606	No	No	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	296.539	-7.554	1.515	90.710	-2.576	No	No	Yes
12	*Z-2-Dodecenol*	184.323	-4.816	1.474	91.684	-1.529	No	No	No
13	*2-Methylenecholestan-3-ol*	400.691	-5.818	1.208	95.328	-2.733	No	No	Yes
14	*L-Alanine*	89.094	-2.887	0.466	81.091	-2.738	No	No	No
15	*levodopa*	197.190	-2.890	-0.289	47.741	-2.735	Yes	No	No
16	*Glycylsarcosine*	146.146	-2.699	0.545	68.130	-2.735	No	No	No
17	*5-Hydroxymethylfurfural*	126.111	-0.590	1.172	95.848	-3.416	No	No	No
18	*10-Undecyn-1-ol*	168.280	-3.892	1.476	93.273	-1.448	No	No	No
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	128.171	-0.757	1.621	97.700	-2.878	No	No	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	206.201	-2.799	0.903	92.210	-2.622	No	No	No

No	Compound	MW	A1	A2	A3	A4	A5	A6	A7
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	212.245	-1.452	1.237	100	-3.221	No	No	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	148.161	-1.632	1.563	100	-3.097	No	No	No

Note: MW = Molecular Weight (g/mol), A1 = Water solubility, A2 = Caco2 permeability, A3 = Intestinal absorption (human), A4 = Skin Permeability, A5 = P-glycoprotein substrate, A6 = P-glycoprotein I inhibitor, A7 = P-glycoprotein II inhibitor.

Table 3. The prediction results of distribution and Excretion properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	D1	D2	D3	D4	E1	E2
1	*15-Chloro-4-pentadecyne*	0.534	0.062	0.917	-1.257	0.557	No
2	*4-(2-Methoxyphenyl)piperidine*	1.122	0.462	0.502	-2.260	0.880	No
3	*Cyclobutanol*	0.047	0.762	-0.031	-2.820	0.448	No
4	*1-Hexadecyne*	0.631	0.067	0.956	-1.364	1.870	No
5	*2-Propylmalonic acid*	-0.936	0.588	-0.060	-3.023	0.444	No
6	*n-Hexadecanoic acid*	-0.543	0.101	-0.111	-1.816	1.763	No
7	*2-Hexylacrylonitrile*	0.260	0.414	0.571	-1.976	0.550	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	0.370	0.234	0.652	-2.093	1.739	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	0.191	0.564	0.447	-2.813	1.266	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	0.531	0.271	0.609	-1.923	0.120	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	0.468	0	0.806	-1.563	1.686	No
12	*Z-2-Dodecenol*	0.358	0.275	0.713	-1.902	1.781	No
13	*2-Methylenecholestan-3-ol*	-0.145	0	0.808	-1.411	0.546	No
14	*L-Alanine*	-0.534	0.473	-0.412	-3.405	0.370	No
15	*levodopa*	-0.105	0.604	-0.843	-3.032	0.430	No
16	*Glycylsarcosine*	-0.680	0.538	-0.614	-3.183	0.217	No
17	*5-Hydroxymethylfurfural*	-0.146	0.744	-0.361	-2.914	0.614	No
18	*10-Undecyn-1-ol*	0.300	0.353	0.721	-1.957	1.713	No

No	Compound	D1	D2	D3	D4	E1	E2
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	-0.007	0.692	0.014	-2.842	0.569	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	0.209	0.207	-0.263	-2.106	0.537	No
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	0.015	0.617	-0.217	-2.909	0.198	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	0.558	0.678	-0.01	-3.357	0.135	No

Note: D1 = VDss (human), D2 = Fraction unbound (human), D3 = BBB permeability, D4 = CNS permeability, E1 = Total Clearance, E2 = Renal OCT2 substrate.

Table 4. The prediction results of metabolism properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	M1	M2	M3	M4	M5	M6	M7
1	*15-Chloro-4-pentadecyne*	No	Yes	Yes	No	No	No	No
2	*4-(2-Methoxyphenyl)piperidine*	No	No	No	No	No	No	No
3	*Cyclobutanol*	No	No	No	No	No	No	No
4	*1-Hexadecyne*	No	Yes	Yes	No	No	No	No
5	*2-Propylmalonic acid*	No	No	No	No	No	No	No
6	*n-Hexadecanoic acid*	No	Yes	No	No	No	No	No
7	*2-Hexylacrylonitrile*	No	No	No	No	No	No	No
8	*3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol*	No	No	No	No	No	No	No
9	*8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione*	No	No	No	No	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	No	No	No	No	No	No	No
11	*3,7,11,15-Tetramethyl-2-hexadecen-1-ol*	No	Yes	Yes	No	No	No	No
12	*Z-2-Dodecenol*	No	No	No	No	No	No	No
13	*2-Methylenecholestan-3-ol*	No	Yes	No	No	No	No	No
14	*L-Alanine*	No	No	No	No	No	No	No
15	*levodopa*	No	No	No	No	No	No	No

No	Compound	M1	M2	M3	M4	M5	M6	M7
16	*Glycylsarcosine*	No	No	No	No	No	No	No
17	*5-Hydroxymethylfurfural*	No	No	No	No	No	No	No
18	*10-Undecyn-1-ol*	No	No	No	No	No	No	No
19	*2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*	No	No	No	No	No	No	No
20	*4-Nitro-5-hydroxy-1,2-dimethylindole*	No	No	Yes	No	No	No	No
21	*9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione*	No	No	No	No	No	No	No
22	*2,7-Dioxa-tricyclo[4.4.0.0(3,8)]deca-4,9-diene*	No	No	No	No	No	No	No

Note: M1 = CYP2D6 substrate, M2 = CYP3A4 substrate, M3 = CYP1A2 inhibitor, M4 = CYP2C19 inhibitor, M5 = CYP2C9 inhibitor, M6 = CYP2D6 inhibitor, M7= CYP3A4 inhibitor.

CONCLUSION

There are 5 compounds predicted to have the best pharmacokinetic properties in *Hemigraphis alternata* leaves, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural* and *2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*. These compounds met the most absorption, distribution and excretion predictors requirements compared to other compounds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YY and RAR conducted the experiment, YY conducted the conceptualization, methodology, formal analysis, writing-review and editing, RAR conducted data curation and writing-original draft preparation.

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Bukti konfirmasi review dan hasil review kedua

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#73117 Review

SUMMARY REVIEW EDITING

Submission

Authors	Yeni Yeni, Rizky Arcinthya Rachmania
Title	The Prediction of Pharmacokinetic Properties of Compounds in *Hemigraphis alternata* (Burm.F.) T. Ander Leaves Using pkCSM
Section	Articles
Editor	Stalis Ethica

Peer Review

Round 1

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No.	The Reviewer's First Comments	Author's Revision	Second Comments
1.	There are some writing errors, such as capitalization not at the beginning of the sentence (for example in fourth sentence abstract), writing abbreviations that have not been preceded by their abbreviations (for examples COX, LOX, ADME, pkCSM in the abstract).	We changed the words COX, LOX, ADME in abstract. There is not definite abbreviation for pkCSM tool, so that we define it in the abstract. *Hemigraphis alternata* is a plant that has anti-inflammatory activity. The compounds contained in *Hemigraphis alternata* leaves have been predicted to have affinity for receptors that play a role in the inflammatory process. A large number of drug candidates were withdrawn from preclinical trials due to their poor pharmacokinetic profiles. Drug compounds must cross the barriers that exist in the body to reach their biological targets so that they can have an effect. The Prediction of pharmacokinetic properties of 22 compounds in *Hemigraphis alternata* leaves was carried out to obtain inflammatory drug candidates that have adequate pharmacokinetic profiles. The application used in this	Writing corrections are not done thoroughly, capitalization not at the beginning of the sentences is still visible in the abstract and the whole article. In addition, the abbreviation must be fully written first (examples COX, LOX).
2.	This study combines several previous studies. However, in the abstract, it is not clear which one was done by other researchers or what was done by the author of this article. For example, as many as 22 secondary metabolites analyzed for their pharmacokinetic profiles using pkCSM in this article are the result of other people's research. Authors may have conducted previous in silico research to see the predictions of these 22 metabolites as anti-inflammatory (but the in silico docking method used and the results of the in silico research did not explain yet). Furthermore, this study actually only determined pharmacokinetic using pkCSM, but this article also wrote conclusions about compounds that have potential as anti-inflammatory (which were not carried out) and also their good pharmacokinetic parameter. As a suggestion, it is better to make a good common thread regarding the research that has been done previously, the results that have been achieved, and its relationship with the research conducted in this article.		The author can't answer the first comment clearly.

		research is pkCSM, a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. The pkCSM used 20 predictors which were divided into 4 properties, absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors) and excretion (2 predictors). Based on the prediction results, there are 5 compounds that have the best pharmacokinetic properties, *8a-Methylhexahydro-1,8(2H,5H)-naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural and 2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*.	
3.	Try using MESH on demand to search for keywords. For the word pharmacokinetic it is recommended to change it to pharmacokinetic parameters/profiles.	**Keywords:** *Hemigraphis alternata*, Pharmacokinetic profiles, pkCSM.	

4.	pkCSM was used as a tool to measure the pharmacokinetic parameters of the secondary metabolite Hemigraphis alternata. Therefore, it is necessary to add in the background section about the pkCSM method (their weaknesses/strengths, and add information on the existence of studies showing a positive correlation of the results of pkCSM with the results of in vivo pharmacokinetic studies).	pkCSM is a tool that can characterize the pharmacokinetic profile of compounds comprehensively. The concept used to predict the predictors by this tool is graph-based structural signatures which train the prediction algorithm by encoding the pattern of distances between atoms. Graphical modeling is the result of an intuitive and well-established mathematical representation of chemical entities. In pkCSM, different predictors including molecular structure and chemistry can be extracted [14–16]. Despite the distribution of experimental values and variability in the size of the data set, pkCSM model was able to achieve a good correlation with experimental results through regression analysis of the ADME predictors [8].	No add information on the existence of studies showing a positive correlation of the results of pkCSM with the results of in vivo pharmacokinetic studies.
5.	In addition to the data for compounds whose pharmacokinetic profile will be determined, the structure of secondary metabolites of Hemigraphis alternata can be drawn in 3D using Chem bio Draw (accompanied by molecular weight information).	We do not put the 3D structure of the compounds but 2D structure and molecular weight information because it considers the need to know the atoms that make up the compounds. See Figure 1.	No citation in figure 1.
6.	Table 1 can be made more comprehensive so that it is easier to understand. You can add a column description of the predicted value for each parameter (for example, the requirements for a good intestinal absorption value > 30/80% and each value can be referenced).	Already fixed. See Table 1.	Table 1 only cites 1 article.
7.	Tables 2, 3 and 4 still have to be given a notes/descriptions under each table (information about the predictor code being analyzed) for	Already fixed See Table 2, 3 and 4.	

	example D1 = ..., D2 = ... in order to make it easier to read the stand-alone table. In column 2, the name of the compound can be given the molecular weight information.		
8.	The predictor values for each pharmacokinetic parameter have been written in table 1, there is no need to discuss it again in the results and discussion section. It is better to discuss how to select compounds (out of a total of 22 compounds) for each parameters (absorption/distribution/metabolism/excretion) based on the results in table 2-4. For example, a compound is selected if it satisfies all of the criteria for predictor values A1-A7 (absorption parameters), or uses only few important predictor categories.	We have deleted the predictor values in discusion and give more information how to analyze the result of pharmacikinetic properties prediction. In this study, the screening process was based on predictors which had a limit value to determine whether or not the pharmacokinetic profile of a compound was good. The predictors included Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3) and CNS permeability (D4). The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54.	The conclusion of choosing a compound that meets the criteria for a pharmacokinetic profile should still be seen from the table presented (table 2-4), for example, by marking which compounds meet the criteria for predictor value. In addition, five selected compound should be highlighted for discussion.
9.	This article need to increase the number of references used	We added 7 references related to this research [10] Brogi, S., Ramalho, T.C., Kuca,	

K., Medina-Franco, J.L. and Valko, M., 2020, In silico methods for drug design and discovery, *Front. Chem*., 8, 612–616.

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		tools in the pharmacokinetic profiles of natural and synthetic compounds with anti-diabetic activity, *Biomolecules*, 11 (11), 1692–1722.	

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#73117 Review

SUMMARY REVIEW EDITING

Submission

Authors	Yeni Yeni, Rizky Arcinthya Rachmania
Title	The Prediction of Pharmacokinetic Properties of Compounds in *Hemigraphis alternata* (Burm.F.) T. Ander Leaves Using pkCSM
Section	Articles
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Peer Review

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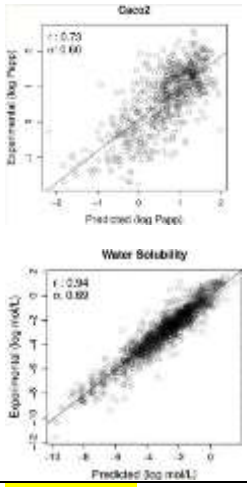
No.	The Reviewer's First Comments	Author's Revision	Second Comments	Second Author's Revision
1.	There are some writing errors, such as capitalization not at the beginning of the sentence (for example in fourth sentence abstract), writing abbreviations that have not been preceded by their abbreviations (for examples COX, LOX, ADME, pkCSM in the abstract).	We changed the words COX, LOX, ADME in abstract. There is not definite abbreviation for pkCSM tool, so that we define it in the abstract. *Hemigraphis alternata* is a plant that has anti-inflammatory activity. The compounds contained in *Hemigraphis alternata* leaves have been predicted to have affinity for receptors that play a role in the inflammatory process. A large number of drug candidates were withdrawn from preclinical trials due to their poor pharmacokinetic profiles. Drug compounds must cross the barriers that exist in the body to reach their biological targets so that they can have an effect. The Prediction of pharmacokinetic properties of 22 compounds in *Hemigraphis alternata* leaves was carried out to obtain inflammatory drug candidates that have adequate pharmacokinetic profiles. The application used in this research is pkCSM, a method for predicting and optimizing the pharmacokinetic properties of small molecules that depend on distance-based graph signatures. The pkCSM used 20 predictors which were divided into 4 properties, absorption (7 predictors), distribution (4 predictors), metabolism (7 predictors) and excretion (2 predictors). Based on the prediction results, there are 5 compounds that have the best pharmacokinetic properties, *8a-Methylhexahydro-1,8(2H,5H)-*	Writing corrections are not done thoroughly, capitalization not at the beginning of the sentences is still visible in the abstract and the whole article. In addition, the abbreviation must be fully written first (examples COX, LOX).	**ABSTRACT** …… …… The pkCSM, a strategy for predicting and optimizing the pharmacokinetic properties of tiny molecules based on distance-based graph signatures was used in this work. The pkCSM employed 20 predictors separated into four groups: absorption, distribution, metabolism, and excretion. Based on the prediction findings, there are five substances with the best pharmacokinetic features, *8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione, (E)-3,7,11,15-tetramethylhexadec-2-en-1-ol, 2-methylenecholestan-3-ol, 5-(hydroxymethyl) furan-2-carbaldehyde* and *2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*. **INTRODUCTION** …… …… This plant's leaves contain 22 secondary metabolites (Figure 1) [5]. These substances exhibit anti-inflammatory effect against cyclooxygenase-1 (COX-1) and 5-lipoxygenase (5-LOX) receptors [6,7]. **EXPERIMENTAL SECTION** **Procedure** …… …… Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), human volume of distribution at steady state (VDss) (D1), Blood-Brain Barrier (BBB) permeability (D3), Central Nervous System (CNS) permeability (D4), and total clearance were the predictors (E1)
2.	This study combines several previous studies. However, in the abstract, it is not clear which one was done by other researchers or what was done by the author of this article. For example, as many as 22 secondary metabolites		The author can't answer the first comment clearly.	We predicted the affinity of these 22 compounds for COX-1, COX-2 and 5-LOX. However, only fof COX-1 has been published (Yeni, Y., Rachmania, R.A. and Mochamad, D.Y.M., 2021, Affinity of

	analyzed for their pharmacokinetic profiles using pkCSM in this article are the result of other people's research. Authors may have conducted previous in silico research to see the predictions of these 22 metabolites as anti-inflammatory (but the in silico docking method used and the results of the in silico research did not explain yet). Furthermore, this study actually only determined pharmacokinetic using pkCSM, but this article also wrote conclusions about compounds that have potential as anti-inflammatory (which were not carried out) and also their good pharmacokinetic parameter. As a suggestion, it is better to make a good common thread regarding the research that has been done previously, the results that have been achieved, and its relationship with the research conducted in this article.	*naphthalenedione, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 2-Methylenecholestan-3-ol, 5-Hydroxymethylfurfural and 2,5-Dimethyl-2,3-dihydro-5H-1,4-dioxepine*.		compounds in Hemigraphis alternata (Burm. F.) T. Ander leaves to cyclooxygenase 1 (COX-1) : In silico approach, in 4th International Conference on Sustainable Innovation 2020–Health Science and Nursing (ICoSIHSN 2020) January, pp. 552–555, Atlantis Press.) and 5-LOX (Yeni, Y., Rachmania, R. and Yanuar , M.D., 2021, In silico study of compounds contained in Hemigraphis alternata leaves against 5-LOX for anti-inflammatory, Indonesia. J. Pharm. Sci. Technol., 8(1),.34–41.). In the abstract and conclusion, we have removed data regarding the predicted affinity of the 22 compounds so that there is no confusion between the results of this study and the results of previous studies. We have previously informed the results of affinity predictions in the introduction section in this article. **INTRODUCTION** …… …… *Hemigraphis alternata* possesses anti-nociceptive, anti-inflammatory and anti-diarrheal effects. In mice, ethyl acetate and methanol extracts of Hemigraphis alternata leaves were found to exhibit anti-inflammatory and non-toxic effects [4]. This plant's leaves contain 22 secondary metabolites (Figure 1) [5]. These substances exhibit anti-inflammatory effect against cyclooxygenase-1 (COX-1) and 5-lipoxygenase (5-LOX) receptors [6,7].
3.	pkCSM was used as a tool to measure the pharmacokinetic parameters of the secondary metabolite Hemigraphis alternata. Therefore, it is necessary to add in the background section about the pkCSM method (their weaknesses/strengths, and add information on the existence of studies showing a positive	pkCSM is a tool that can characterize the pharmacokinetic profile of compounds comprehensively. The concept used to predict the predictors by this tool is graph-based structural signatures which train the prediction algorithm by encoding the pattern of distances between atoms. Graphical modeling is the result of an intuitive and well-established mathematical	No add information on the existence of studies showing a positive correlation of the results of pkCSM with the results of in vivo pharmacokinetic studies.	We informed that there is a good correlation between the ADME predictions of pkCSM and the experimental results in the following paragraphs: **INTRODUCTION** …… …….. Different predictors, including molecular structure and chemistry

	correlation of the results of pkCSM with the results of in vivo pharmacokinetic studies).	representation of chemical entities. In pkCSM, different predictors including molecular structure and chemistry can be extracted [14–16]. Despite the distribution of experimental values and variability in the size of the data set, pkCSM model was able to achieve a good correlation with experimental results through regression analysis of the ADME predictors [8].		may be retrieved using pkCSM [14–16]. Despite the diversity in the size of the data set and the distribution of experimental values, the pkCSM model was able to establish a strong correlation with experimental results through regression analysis of the ADME predictors [8]. In reference [8], the results of regression analysis for absorption predictors are shown considering cross-validation schemes. Pearson's correlation coefficients and standard error are also shown at the top-left corner. The first graph shows the correlation between experimental and predicted values for Caco2 permeability, while the second graph for water solubility. 
4.	In addition to the data for compounds whose pharmacokinetic profile will be determined, the structure of secondary metabolites of Hemigraphis alternata can be drawn in 3D using Chem bio Draw (accompanied by molecular weight information).	We do not put the 3D structure of the compounds but 2D structure and molecular weight information because it considers the need to know the atoms that make up the compounds. See Figure 1.	No citation in figure 1.	**Figure 1**. The compounds contained in Hemigraphis alternata leaves [6,7].
5.	Table 1 can be made more comprehensive so that it is easier to understand. You can add a column description of the predicted value for each parameter (for example, the requirements for a good intestinal absorption value > 30/80% and each value can be referenced).	Already fixed. See Table 1.	Table 1 only cites 1 article.	In Table 1, there are predictors and their limitations used in this study based on only 1 recommended reference on the pkCSM website (http://biosig.unimelb.edu.au/pkcsm/theory).
6.	The predictor values for each pharmacokinetic parameter have been	We have deleted the predictor values in discusion and give more information how to	The conclusion of choosing a compound that	Table 2-4 highlights the conclusions on the selection of compounds

	written in table 1, there is no need to discuss it again in the results and discussion section. It is better to discuss how to select compounds (out of a total of 22 compounds) for each parameters (absorption/distribution/metabolism/excretion) based on the results in table 2-4. For example, a compound is selected if it satisfies all of the criteria for predictor values A1-A7 (absorption parameters), or uses only few important predictor categories.	analyze the result of pharmacikinetic properties prediction. In this study, the screening process was based on predictors which had a limit value to determine whether or not the pharmacokinetic profile of a compound was good. The predictors included Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3) and CNS permeability (D4). The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54.	meets the criteria for a pharmacokinetic profile should still be seen from the table presented (table 2-4), for example, by marking which compounds meet the criteria for predictor value. In addition, five selected compound should be highlighted for discussion.	that match the pharmacokinetic profile requirements. The following five compounds are mentioned in this section: **RESULTS AND DISCUSSION** …… …… Therefore, the compounds 9 (8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione), 11 ((E)-3,7,11,15-tetramethylhexadec-2-en-1-ol), 13 (2-methylenecholestan-3-ol), 17 (5-(hydroxymethyl) furan-2-carbaldehyde) and 19 (2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin) can be used as anti-inflammatory drug candidates that have good ADME because these compounds are intersection which meet the requirements of absorption, distribution and excretion predictors. Prediction of the metabolism properties of these 22 compounds provides information about the possibility of these compounds being metabolized in the liver. There are 2 compounds from 5 virtual screening compounds that are predicted to be metabolized in the liver. Compound 11 is a CYP3A4 substrate (M2) and a CYP1A2 inhibitor (M3), while compound 13 is a CYP3A4 substrate (M2) (Table 4). The basic structures of the five drugs projected to have favorable pharmacokinetic characteristics differ. However, several of them share the same substituents. Compounds 9, 11, 13, and 19 all contain methyl substituents. Compounds 11, 13, and 17 all contain hydroxyl substituents.

THE PREDICTION OF PHARMACOKINETIC PROPERTIES OF COMPOUNDS IN HEMIGRAPHIS ALTERNATA (BURM.F.) T. ANDER LEAVES USING PKCSM

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ABSTRACT

The inflammatory process aids in healing and maintains the body's balance. Untreated acute inflammation can cause organ disease, which can lead to a chronic inflammatory phenotype. *Hemigraphis alternata* is a plant that has anti-inflammatory activity. The compounds contained in *Hemigraphis alternata* leaves have been predicted to have affinity for receptors involved in the inflammatory process. A large number of drug candidates were withdrawn from preclinical trials due to their poor pharmacokinetic profiles. Drug compounds must cross the barriers that exist in the body to reach their biological targets so that they can have an effect. The pharmacokinetic features of 22 components in *Hemigraphis alternata* leaves were predicted in order to produce inflammatory medication candidates with suitable pharmacokinetic profiles. The pkCSM, a strategy for predicting and optimizing the pharmacokinetic properties of tiny molecules based on distance-based graph signatures was used in this work. The pkCSM employed 20 predictors separated into four groups: absorption, distribution, metabolism, and excretion. Based on the prediction findings, there are five substances with the best pharmacokinetic features, *8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione, (E)-3,7,11,15-tetramethylhexadec-2-en-1-ol, 2-methylenecholestan-3-ol, 5-(hydroxymethyl) furan-2-carbaldehyde* and *2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*.

Keywords: *Hemigraphis alternata*, Pharmacokinetic profiles, pkCSM.

INTRODUCTION

Inflammation is the body's defensive reaction to potentially hazardous impulses such as viruses or chemicals that induce cell injury. It triggers inflammatory cells and signaling pathways. The process of inflammation is critical in the recovery process because it allows aberrant bodily homeostasis to be restored. Acute inflammation that is not effectively managed can aggravate organ disease and eventually develop to a chronic inflammatory phenotype [1–3].

Hemigraphis alternata possesses anti-nociceptive, anti-inflammatory and anti-diarrheal effects. In mice, ethyl acetate and methanol extracts of *Hemigraphis alternata* leaves were found to exhibit anti-inflammatory and non-toxic effects [4]. This plant's leaves contain 22 secondary

metabolites (**Figure 1**) [5]. These substances exhibit anti-inflammatory effect against cyclooxygenase-1 (COX-1) and 5-lipoxygenase (5-LOX) receptors [6,7].

The interaction of pharmacokinetic characteristics, toxicity, and potency has a significant impact on a drug's efficacy. A compound's pharmacokinetic profiles are determined to assess its absorption, distribution, metabolism and excretion (ADME) features [8]. The preliminary evaluation of ADME features will assist pharmaceutical researchers in selecting the best medication candidates for development and rejecting drug candidates with a poor likelihood of success [9]. The creation of novel drug candidates is a difficult, time-consuming and expensive procedure. In the development of novel medications, in silico computational model plays an essential role. Its use reduces the amount of time and resources needed for the rational design of novel medication candidates. Pharmaceutical advancements have raised the necessity for more accurate methodologies to predict the pharmacokinetic features of novel drug candidates. Because of the improvement of computer algorithms and massive information databases, computational prediction tools are increasingly routinely employed in the procedure for drug discovery. Furthermore, in silico technologies have been employed in the discovery of various drugs that are now used in the treatment of disorders [10–13].

The application of pkCSM is a tool that can characterize the pharmacokinetic profile of compounds comprehensively. The concept used to predict the predictors by this tool is graph-based structural signatures which train the prediction algorithm by encoding the pattern of distances between atoms. Graphical modeling is the consequence of an understandable and well-established mathematical description of chemical entities. Different predictors, including molecular structure and chemistry may be retrieved using pkCSM [14–16]. Despite the diversity in the size of the data set and the distribution of experimental values, the pkCSM model was able to establish a strong correlation with experimental results through regression analysis of the ADME predictors [8]. The mission of in silico ADME prediction is to accurately forecast the in vivo pharmacokinetic features of prospective therapeutic compounds in humans using only virtual structures. In silico analysis was used to estimate the pharmacokinetic features of 22 chemicals found in *Hemigraphis alternata* leaves.

EXPERIMENTAL SECTION

Include enough information to allow the work to be repeated, such as materials, instruments, and processes.

Materials

PubChem (pubchem.ncbi.nlm.nih.gov) provided the SMILES format of 22 chemicals found in the leaves of *Hemigraphis alternata*. The SMILES translator, cactus in https://cactus.nci.nih.gov can be used to get compounds that do not have the SMILES format in PubChem.

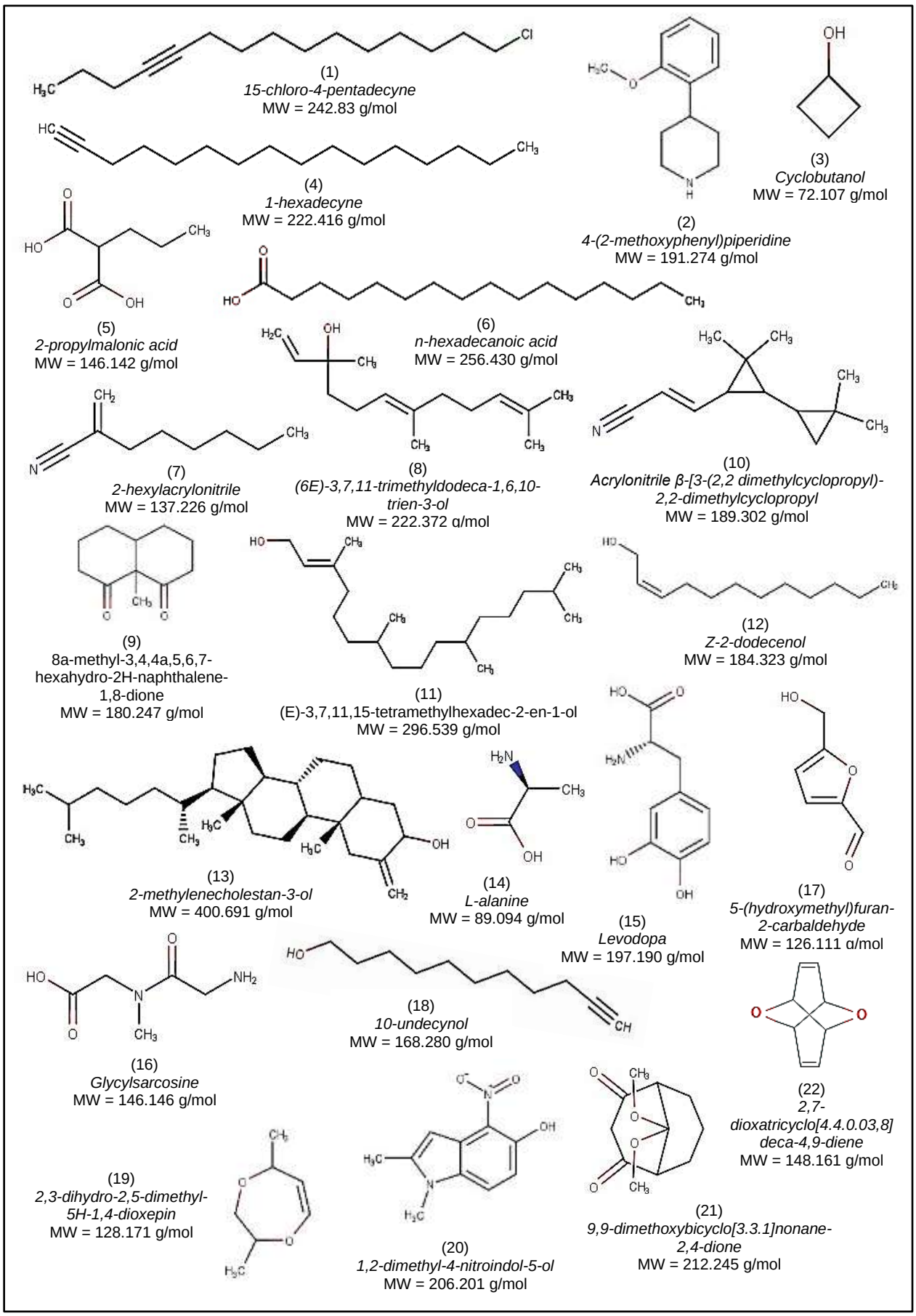

Figure 1. The compounds contained in *Hemigraphis alternata* leaves [6,7].

Instrumentation

The pharmacokinetic characteristics of 22 chemicals in the leaves of *Hemigraphis alternata* were estimated using pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction).

Procedure

The application of pkCSM is based on compound general qualities (molecular properties, toxicophores, and pharmacophores), as well as distance-based graph signatures. In pkCSM there are 20 predictors that describe the pharmacokinetic properties of a compound. The predictors were divided into absorption of 7 predictors, distribution of 4 predictors, metabolism of 7 predictors and excretion of 2 predictors (**Table 1**) [8,17,18].

Table 1. Distribution of ADME predictors in pkCSM [8]

Pharmacokinetic Parameter	Predictor (Code)	Unit	Requirement value
Absorption	Water solubility (A1)	log mol/L	-
	Caco2 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	-

Pharmacokinetic Parameter	Predictor (Code)	Unit	Requirement value
	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	-

In this study, virtual screening was carried out to obtain several compounds that had good ADME. The findings of the ADME predictor, which has a numerical value with specific constraints, are used in virtual screening. Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), human volume of distribution at steady state (VDss) (D1), Blood-Brain Barrier (BBB) permeability (D3), Central Nervous System (CNS) permeability (D4), and total clearance were the predictors (E1) [19].

Initially, test compounds were selected based on predictors of Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3) and CNS permeability (D4). The compounds that meet the requirements will be re-screened based on the highest total clearance (E1) value [8].

RESULTS AND DISCUSSION

The use of pkCSM is a strategy for estimating and improving the pharmacokinetic characteristics of small compounds based on distance-based graph signatures. The use of pkCSM extends the cutoff scanning idea to depict molecular and chemical structures in order to characterize and predict their pharmacokinetic features. [8].

Water solubility is an essential aspect in a drug's pharmacological reaction following oral delivery. Drugs with strong water solubility will have good absorption and bioavailability qualities. Drug absorption and bioavailability can boost plasma drug concentrations at the target location, allowing it to fulfill therapeutic actions [20].

Caco-2 cells are a kind of colorectal cancer cell line [21]. In pre-clinical studies, the Caco-2 model was utilized to predict medication gastrointestinal permeability. Based on the properties of the human small intestine, this model expresses enterocytes, transporters, cytochrome P450 enzymes and microvilli [22]. A compound's Caco-2 permeability is high if its Papp is more than 8 x 10-6 cm/s.

The gut is the primary location of oral medication absorption. The skin serves as a barrier between the interior and exterior environments of the body. Skin qualities and traits can vary and influence medication distribution and toxicity [23]. The skin permeability constant log Kp (cm/hour) expresses a compound's likelihood to be skin permeable.

P-glycoprotein (P-gp) is an ATP-binding cassette (ABC) transporter that acts as a biological barrier in cells by eliminating toxins and xenobiotics. The ability of a chemical to block the transport of P-gp I and P-gp II is referred to as P-gp I/II inhibitor. P-gp-mediated transport modification has important pharmacokinetic consequences for P-gp substrates. Inhibiting P-gp I or P-gp II might provide therapeutic benefits or result in contraindications [8].

VDss (human) is calculated by dividing all drug inside the body by drug concentration in plasma in stable state. This state happens when the system receives a consistent rate of medication infusion into the plasma and all drug concentrations in the body remain constant [24]. The capacity of a medicine to bind proteins in the blood can have an impact on its efficacy. The greater the proportion of the drug that is not bound to protein (fraction unbound), the more effectively the medication will cross or diffuse through the cell membrane [8].

Increased permeability of the BBB, a physical and biochemical barrier that plays a role in the protection of cerebral homeostasis, can alter the pathological development of ischemic tissue [25,26]. The value of the blood-brain permeability surface area product can be used to estimate a pharmacological compound's capacity to reach the CNS (log PS). This value was achieved through in situ brain perfusion with the chemical directly injected into the carotid artery without any systemic distribution impact that may skew brain penetration [8].

Cytochrome P450 is a detoxifying enzyme present in the liver. In general, cytochrome P450 is involved in drug metabolism. However, P450 inhibitors can significantly affect medication pharmacokinetics. As a result, it is critical to determine if the provided molecule is a CYP2D6/CYP3A4 substrate expected to be processed by P450. Cytochrome P450 oxidizes xenobiotics so that they can be excreted. Many medications are inactivated by cytochrome P450, whereas others might be activated by it. These enzyme inhibitors have the potential to interfere with medication metabolism and are thus not recommended. It is therefore critical to evaluate the compound's capacity to inhibit cytochrome P450 (isoforms CYP1A2/CYP2C19/CYP2C9/CYP2D6/ CYP3A4). A substance is termed a cytochrome P450 inhibitor if the concentration required to achieve 50% inhibition is less than 10 M. [8].

The amount of drug removed from plasma in the vascular compartment per unit time is referred to as drug clearance. Total clearance is the result of all body clearances. Total clearance indicates drug removal from the core compartment without regard for the process mechanism [27]. The renal uptake transporter Organic Cation Transporter 2 (OCT2) is crucial for disposition of drugs and renal clearance. When used with OCT2 inhibitors, OCT2 substrates might have negative side effects [8].

In the results of the prediction of absorption properties obtained compounds 3, 6, 9, 11, 13, 17, 19, 20, 21 and 22 which are in accordance with the requirements (**Table 2**). Meanwhile, the compounds that meet the requirements for distribution and excretion properties are compounds 1, 2, 4, 7, 8, 9, 11, 12, 13, 17, 18, and 19 (**Table 3**). Therefore, the compounds 9 (*8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione*), 11 (*(E)-3,7,11,15-tetramethylhexadec-2-en-1-ol*), 13 (*2-methylenecholestan-3-ol*), 17 (*5-(hydroxymethyl) furan-2-carbaldehyde*) and 19 (*2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*) can be used as anti-inflammatory drug candidates that have good ADME because these compounds are intersection which meet the requirements of absorption, distribution and excretion predictors. Prediction of the metabolism properties of these 22 compounds provides information about the possibility of these compounds being metabolized in the liver. There are 2 compounds from 5 virtual screening compounds that are predicted to be metabolized in the liver. Compound 11 is a CYP3A4 substrate (M2) and a CYP1A2 inhibitor (M3), while compound 13 is a CYP3A4 substrate (M2) (**Table 4**). The basic structures of the five drugs projected to have favorable pharmacokinetic characteristics differ. However, several of them share the same substituents. Compounds 9, 11, 13, and 19 all contain methyl substituents. Compounds 11, 13, and 17 all contain hydroxyl substituents. In this study, the screening process was based on predictors which had a limit value to determine whether or not the pharmacokinetic profile of a compound was good. The predictors included Caco2 permeability (A2), intestinal absorption (human) (A3), skin permeability (A4), VDss (human) (D1), BBB permeability (D3) and CNS permeability (D4). The results of the virtual screening were then sorted based on the highest total clearance value (E1) log ml/min/kg, in this study ≥ 0.54.

Table 2. The prediction results of absorption properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	MW	A1	A2	A3	A4	A5	A6	A7
1	*15-chloro-4-pentadecyne*	242.830	-7.634	1.402	92.577	-2.420	No	No	No
2	*4-(2-methoxyphenyl)piperidine*	191.274	-1.835	1.385	91.872	-2.283	No	No	No
3	*Cyclobutanol*	72.107	0.092	1.463	98.450	-3.027	Yes	No	No
4	*1-hexadecyne*	222.416	-7.801	1.382	92.797	-2.225	No	No	No
5	*2-propylmalonic acid*	146.142	-1.323	0.667	74.589	-2.735	No	No	No

No	Compound	MW	A1	A2	A3	A4	A5	A6	A7
6	*n-hexadecanoic acid*	256.430	-5.562	1.558	92.004	-2.717	No	No	No
7	*2-hexylacrylonitrile*	137.226	-3.861	1.357	94.383	-1.278	No	No	No
8	*(6E)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol*	222.372	-5.176	1.498	91.887	-1.477	No	No	No
9	*8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione*	180.247	-2.187	1.605	97.468	-2.814	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	189.302	-4.729	1.382	95.941	-1.606	No	No	No
11	*(E)-3,7,11,15-tetramethylhexadec-2-en-1-ol*	296.539	-7.554	1.515	90.710	-2.576	No	No	Yes
12	*Z-2-dodecenol*	184.323	-4.816	1.474	91.684	-1.529	No	No	No
13	*2-methylenecholestan-3-ol*	400.691	-5.818	1.208	95.328	-2.733	No	No	Yes
14	*L-alanine*	89.094	-2.887	0.466	81.091	-2.738	No	No	No
15	*Levodopa*	197.190	-2.890	-0.289	47.741	-2.735	Yes	No	No
16	*Glycylsarcosine*	146.146	-2.699	0.545	68.130	-2.735	No	No	No
17	*5-(hydroxymethyl)furan-2-carbaldehyde*	126.111	-0.590	1.172	95.848	-3.416	No	No	No
18	*10-undecynol*	168.280	-3.892	1.476	93.273	-1.448	No	No	No
19	*2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*	128.171	-0.757	1.621	97.700	-2.878	No	No	No
20	*1,2-dimethyl-4-nitroindol-5-ol*	206.201	-2.799	0.903	92.210	-2.622	No	No	No
21	*9,9-dimethoxybicyclo[3.3.1]nonane-2,4-dione*	212.245	-1.452	1.237	100	-3.221	No	No	No
22	*2,7-dioxatricyclo[4.4.0.03,8]deca-4,9-diene*	148.161	-1.632	1.563	100	-3.097	No	No	No

Note: ▒ = The compounds that satisfy the requirement values, MW = Molecular Weight (g/mol), A1 = Water solubility, A2 = Caco2 permeability, A3 = Intestinal absorption (human), A4 = Skin Permeability, A5 = P-glycoprotein substrate, A6 = P-glycoprotein I inhibitor, A7 = P-glycoprotein II inhibitor.

Table 3. The prediction results of distribution and excretion properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	D1	D2	D3	D4	E1	E2
1	*15-chloro-4-pentadecyne*	0.534	0.062	0.917	-1.257	0.557	No
2	*4-(2-methoxyphenyl)piperidine*	1.122	0.462	0.502	-2.260	0.880	No
3	*Cyclobutanol*	0.047	0.762	-0.031	-2.820	0.448	No
4	*1-hexadecyne*	0.631	0.067	0.956	-1.364	1.870	No
5	*2-propylmalonic acid*	-0.936	0.588	-0.060	-3.023	0.444	No
6	*n-hexadecanoic acid*	-0.543	0.101	-0.111	-1.816	1.763	No
7	*2-hexylacrylonitrile*	0.260	0.414	0.571	-1.976	0.550	No
8	*(6E)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol*	0.370	0.234	0.652	-2.093	1.739	No
9	*8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione*	0.191	0.564	0.447	-2.813	1.266	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	0.531	0.271	0.609	-1.923	0.120	No
11	*(E)-3,7,11,15-tetramethylhexadec-2-en-1-ol*	0.468	0	0.806	-1.563	1.686	No
12	*Z-2-dodecenol*	0.358	0.275	0.713	-1.902	1.781	No
13	*2-methylenecholestan-3-ol*	-0.145	0	0.808	-1.411	0.546	No
14	*L-alanine*	-0.534	0.473	-0.412	-3.405	0.370	No
15	*Levodopa*	-0.105	0.604	-0.843	-3.032	0.430	No
16	*Glycylsarcosine*	-0.680	0.538	-0.614	-3.183	0.217	No
17	*5-(hydroxymethyl)furan-2-carbaldehyde*	-0.146	0.744	-0.361	-2.914	0.614	No
18	*10-undecynol*	0.300	0.353	0.721	-1.957	1.713	No
19	*2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*	-0.007	0.692	0.014	-2.842	0.569	No
20	*1,2-dimethyl-4-nitroindol-5-ol*	0.209	0.207	-0.263	-2.106	0.537	No
21	*9,9-dimethoxybicyclo[3.3.1]nonane-2,4-dione*	0.015	0.617	-0.217	-2.909	0.198	No

No	Compound	D1	D2	D3	D4	E1	E2
22	*2,7-dioxatricyclo[4.4.0.03,8]deca-4,9-diene*	0.558	0.678	-0.01	-3.357	0.135	No

Note: ▒ = The compounds that satisfy the requirement values, D1 = VDss (human), D2 = Fraction unbound (human), D3 = BBB permeability, D4 = CNS permeability, E1 = Total Clearance, E2 = Renal OCT2 substrate.

Table 4. The prediction results of metabolism properties 22 compounds contained in *Hemigraphis alternata* using pkCSM

No	Compound	M1	M2	M3	M4	M5	M6	M7
1	*15-chloro-4-pentadecyne*	No	Yes	Yes	No	No	No	No
2	*4-(2-methoxyphenyl)piperidine*	No	No	No	No	No	No	No
3	*Cyclobutanol*	No	No	No	No	No	No	No
4	*1-hexadecyne*	No	Yes	Yes	No	No	No	No
5	*2-propylmalonic acid*	No	No	No	No	No	No	No
6	*n-hexadecanoic acid*	No	Yes	No	No	No	No	No
7	*2-hexylacrylonitrile*	No	No	No	No	No	No	No
8	*(6E)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol*	No	No	No	No	No	No	No
9	*8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione*	No	No	No	No	No	No	No
10	*Acrylonitrile β-[3-(2,2 dimethylcyclopropyl)-2,2-dimethylcyclopropyl*	No	No	No	No	No	No	No
11	*(E)-3,7,11,15-tetramethylhexadec-2-en-1-ol*	No	Yes	Yes	No	No	No	No
12	*Z-2-dodecenol*	No	No	No	No	No	No	No
13	*2-methylenecholestan-3-ol*	No	Yes	No	No	No	No	No
14	*L-alanine*	No	No	No	No	No	No	No
15	*Levodopa*	No	No	No	No	No	No	No
16	*Glycylsarcosine*	No	No	No	No	No	No	No
17	*5-(hydroxymethyl)furan-2-carbaldehyde*	No	No	No	No	No	No	No
18	*10-undecynol*	No	No	No	No	No	No	No
19	*2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*	No	No	No	No	No	No	No

No	Compound	M1	M2	M3	M4	M5	M6	M7
20	*1,2-dimethyl-4-nitroindol-5-ol*	No	No	Yes	No	No	No	No
21	*9,9-dimethoxybicyclo[3.3.1]nonane-2,4-dione*	No	No	No	No	No	No	No
22	*2,7-dioxatricyclo[4.4.0.03,8]deca-4,9-diene*	No	No	No	No	No	No	No

Note: = The selected compounds, M1 = CYP2D6 substrate, M2 = CYP3A4 substrate, M3 = CYP1A2 inhibitor, M4 = CYP2C19 inhibitor, M5 = CYP2C9 inhibitor, M6 = CYP2D6 inhibitor, M7= CYP3A4 inhibitor.

CONCLUSION

There are five chemicals in *Hemigraphis alternata* leaves that are projected to have the best pharmacokinetic qualities, *8a-methyl-3,4,4a,5,6,7-hexahydro-2H-naphthalene-1,8-dione, (E)-3,7,11,15-tetramethylhexadec-2-en-1-ol, 2-methylenecholestan-3-ol, 5-(hydroxymethyl) furan-2-carbaldehyde* and *2,3-dihydro-2,5-dimethyl-5H-1,4-dioxepin*. These compounds met the most absorption, distribution and excretion predictors requirements compared to other compounds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YY and RAR conducted the experiment, YY conducted the conceptualization, methodology, formal analysis, writing-review and editing, RAR conducted data curation and writing-original draft preparation.

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Abstract	*The inflammatory process aids in healing and maintains the body's balance. Untreated acute inflammation can cause organ disease, which can lead to a chronic inflammatory phenotype.* Hemigraphis alternata *is a plant that has anti-inflammatory activity. The compounds contained in H. alternata leaves have been predicted to have an*