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Physicochemical and Pharmacokinetic Property Prediction of Substances in *Centella asiatica* using pkCSM: Prospects for the Creation of Therapeutic Formulations from Plant Isolates

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ABSTRACT

Indonesia is a megabiodiversity country with the second-largest abundance of biodiversity in the world. *Centella asiatica* (CA) is an important medicinal herb used in various countries in the world. It is known to have good pharmacological activity, but more scientific data is still needed to justify its increasing use, especially regarding its pharmacokinetics and safety. The aim of the research was to predict the physicochemical and pharmacokinetic properties of the compounds contained in CA. The compound content was obtained from journal references that collected information from Dr. Duke's Phytochemical and Ethnobotanical Database, then each compound was subjected to physicochemical and pharmacokinetic analysis using a web tool. The results show that the compounds quercetin and kaempferol are compounds that have good physicochemical and pharmacokinetic properties compared to other compounds contained in CA.

INTRODUCTION

Indonesia is a country with the second largest abundance of biodiversity, including a megabiodiversity country (Putra et al., 2012; Rosana 2019). Located between two continents, Asia and Australia, and between two oceans, the Indian and the Pacific (Nugroho et al., 2022), Indonesia has various types of living creatures both on land and in the water with their uniqueness. Although it covers only 1.3% of the world's total land area, the country has enormous biological riches, including 10% of the world's flowering plant species, 12% of the world's mammals, 16% of the world's reptiles & amphibians, 17% of the world's birds, and 25% of the world's fish. world. Unfortunately, currently, biodiversity is threatened by various factors including global climate change and human invasion which causes environmental damage (Occhipinti-Ambrogi, 2003; Rosana 2019).

Indonesia's natural wealth of plants involves 30,000 plant species out of a total of 40,000 plant species in the world, with 940 of them being medicinal plants. The use of local plants as a source of medicine is an alternative that can be developed, because medicinal plants can be an option for treating various types of diseases. Moreover, the side effects resulting from the use of traditional (herbal) medicines tend to be smaller compared to the use of synthetic and chemical (modern) medicines (Anwar, 2013).

Indonesian people have long known about the use of plants as medicine, especially in rural areas. Local people in rural areas have good knowledge about the use of plants and prefer medicinal plants because of their abundant availability and cheaper prices compared to modern medicines. This preference forms local wisdom. Basic Health Research Data (Ris-kesdas) in 2013 shows that 35.2% of Indonesian people still maintain and use traditional medicine for treatment (Shanthi et al., 2014).

Centella asiatica (CA) is an important medicinal herb used in Eastern countries (Bown, 1995) and has become popular in the West (Chevallier, 1996). Known as mandukparni or Indian pennywort, CA has been used as a medicine in the Indian Ayurvedic tradition for thousands of years and is listed in the 'Sushruta Samhita,' an ancient Indian medical text. This herb is also used by the people of Java and other islands in Indonesia, while in China it is known as gotu kola, one of the “miraculous elixirs of life” reported more than 2000 years ago (Diwan et al., 1991; Jamil and Saputro, 2023).

In the nineteenth century, CA and its extracts were included in the Indian pharmacopoeia, where apart from wound healing, CA was also recommended for the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhea, fever, amenorrhea, and diseases of the female genitourinary tract (Jamil and Saputro, 2023). Although many studies have been reported over the past decades regarding the evaluation of biologically active components and their mechanisms of action, the results of these studies are still not satisfactory. Although there are several claims regarding the mechanisms underlying the biological actions of this herb, more scientific data is needed to justify its increasing use, especially regarding its pharmacokinetics and safety. This review was carried out to analyse the

physicochemical and pharmacokinetic properties, including Adsorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) of the compounds contained in CA.

THEORETICAL REVIEW

The compound content in *Centella asiatica* (CA) was obtained from journal references that collected information from Dr. Duke's Phytochemical and Ethnobotanical Database (https://phytochem.nal.usda.gov/phytochem/search). Data collected from this database is strengthened by information accessed from the PubChem chemical compound library portal (https://pubchem.ncbi.nlm.nih.gov/). Complete chemical compound data includes SMILES (Simplecular-Input Line-Entry System) data (Jamil and Saputro, 2023). Details of the compounds collected can be found in Table 1.

METHODOLOGY

Table 1. Compounds of *Centella asiatica*

Compound name	SMILES Code
Centellin	CCCCC/C=C/C(C#CC(C=C)O)OC(=O)C
Centellicin	CC#CCCC(CC/C(=C/C(=O)OCCCO)/C)OC#C
Madecassic acid	C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@H]4[C@]3(C[C@H]([C@@H]5[C@@]4(C[C@H]([C@@H]([C@@]5(C)CO)O)O)C)O)C)[C@@H]2[C@H]1C)C)C(=O)O
Madasiatic acid	CC1CCC2(CCC3(C(=CCC4C3(CC(C5C4(CC(C(C5(C)C)O)O)C)O)C)C2C1C)C)C(=O)O
Isothankunic acid	CC1CCC2(CCC3(C(=CCC4C3(CC(C5(C4(CCC(C5(C)CO)O)C)O)O)C)C2C1C)C)C(=O)O
Pomolic acid	C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]5[C@@]4(CC[C@@H](C5(C)C)O)C)C)[C@@H]2[C@]1(C)O)C)C(=O)O
2alpha-hydroxyursolic acid	C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]5[C@@]4(C[C@H]([C@@H](C5(C)C)O)O)C)C)[C@@H]2[C@H]1C)C)C(=O)O
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Kaempferol	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O

Next, physicochemical and pharmacokinetic analyzes were carried out using the pkCSM web tool (https://biosig.lab.uq.edu.au/pkcsm/prediction) by entering the SMILES code of each compound. After entering the SMILES code, you can click the "ADMET" option on the pkCSM platform, and then wait until the analysis process is complete. This process will provide useful information regarding the adsorption, distribution, metabolism, excretion and toxicity (ADMET) properties of these compounds.

RESULTS

The pkCSM is a method used to predict and optimize the pharmacokinetic and toxicity properties of small molecules that rely on distance-based graphic signatures (Pires et al., 2015). This evaluation was conducted in accordance with Lipinski's rules of five, with specific parameters outlined in Table 2. Lipinski's parameters include HBD <5, HBA <10, log P <5, and molecular weight <500 g/mol (Ma'arif et al., 2022a; Muslikh et al., 2022). Compounds with a molecular weight <500 g/mol may possess the capability to traverse biological membranes (Ma'arif et al., 2022b). The H-acceptor and H-donor values signify the number of hydrogen bonds within the compound. Higher values for these parameters indicate an increased energy requirement during the absorption process (Muslikh et al., 2023). The log P value represents the compound's solubility in membrane fluid and reflects its polarity (Lipinski et al., 1997; Ma'arif et al., 2022c). The topological polar surface area (TPSA) value denotes the compound's ability to penetrate the cell membrane of the body (Ma'arif et al., 2021).

Table 2. Physicochemical properties of compounds

Compound name	Physicochemical properties				
	Molecular weight	Log P	Num. H-bond acceptors (HBA)	Num. H-bond donors (HBD)	TPSA
Centellin	250,338	2,6049	3	1	109,538
Centellicin	294,391	2,0523	4	2	127,757
Madecassic acid	504,708	4,0035	5	5	215,737
Madasiatic acid	488,709	5,0311	4	4	210,942
Isothankunic acid	504,708	4,1476	5	5	215,737
Pomolic acid	472,710	6,2044	3	3	206,148
2alpha-hydroxyursolic acid	472,710	6,0603	3	3	206,148
Quercetin	302,238	1,9880	7	5	122,108
Kaempferol	286,239	2,2824	6	4	117,313

NB: The red color block is a compound that does not fit into the criteria

The pharmacokinetic test results revealed that both quercetin and kaempferol exhibited favorable absorption properties, meeting the criteria for penetration through CaCO2 permeability, absorption in the human intestine, and high permeability in the skin (refer to Table 3). Additionally, in terms of distribution parameters, both compounds demonstrated the ability to be distributed in the network with a range of 0.45 > VDSS < -0.15. Furthermore, they demonstrated the capability to cross the blood-brain barrier (BBB) and the central nervous system (CNS), suggesting their potential as drug candidates targeting the central nervous system (Gondokesumo et al., 2024).

Regarding metabolism parameters, the assessment of indicators for inhibiting and metabolizing cytochrome P450 showed varying results. Both compounds were identified as potential CYP2D6 and CYP3A4 substrates. These two compounds only have inhibition against CYP1A2 inhibitors.

Parameter	Centellin	Centellicin	Quercetin	Kaempferol	Indicators
Absorption					
CaCO2 permeability (log Papp in 10 $^{-6}$ cm/s)	1,414	0.895	-0.229	0.032	High CaCO2 permeability would value >0.90
Intestinal absorption (human) (% Absorbed)	94,924	93,278	77,207	74,290	Poor absorption, if < 30%
Skin permeability (log Kp)	-2,406	-3,29	-2,735	-2,735	Low, if log Kp > -2.5
Distributions					
VDSS (human) (log L/kg)	-0.056	-0.139	1,559	1,274	Low, if log < -0.15 High, if log > 0.45
BBB permeability (log BB)	-0.160	-0.509	-1,098	-0.939	Good, if logBB > 0.3 Poor, if logBB < -1
CNS permeability (log PS)	-2,252	-2,954	-3,065	-2,228	Can penetrate, if Log PS > -2 Cannot penetrate, if Log PS < -3
Metabolism					
CYP2D6 Substrates	No	No	No	No	Yes/No
CYP3A4 Substrates	No	No	No	No	Yes/No
CYP1A2 inhibitors	No	No	Yes	Yes	Yes/No
CYP2C19 inhibitors	No	No	No	No	Yes/No
CYP2C9 inhibitors	No	No	No	No	Yes/No
CYP2D6 inhibitors	No	No	No	No	Yes/No
CYP3A4 inhibitors	No	No	No	No	Yes/No
Excretion					

Total clearances	1,920	1,852	0,407	0,477	Higher is better
Renal OCT2 substrates	No	Yes	No	No	Yes/No
Toxicity					
AMES toxicity	No	No	No	No	Yes/No
Max. tolerated dose (human) (log mg/kg/day)	0.342	0.522	0.499	0.531	-
hERG I inhibitors	No	No	No	No	Yes/No
hERG II inhibitors	No	No	No	No	Yes/No
Hepatotoxicity	No	No	No	No	Yes/No
Skin Sensitization	Yes	No	No	No	Yes/No
***T. Pyriformis* toxicity (log ug/L)**	1,718	1,148	0.288	0.312	Toxic, if Log > 0.5 ug/L
Minnow toxicity (log mM)	0.961	1,358	3,721	2,885	The acute toxicity is high, if Log < - 0.3

NB: The red color block is a compound that does not fit into the criteria

Toxicity is a crucial parameter in drug candidate design, and the toxicity test results indicated that both compounds were non-toxic (Pires et al., 2015). In terms of excretion analysis, it was observed that kaempferol had a higher total clearance value than quercetin, signifying a greater excretion rate for kaempferol. Notably, both compounds were not classified as Renal OCT2 substrates, indicating their non-toxic effects in oral preparations when consumed alongside renal OCT2 inhibitors (Pires et al., 2015).

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a type of flavonoid which is presentcommonly in various foods including fruits, and vegetable (Baghel et al., 2012). Quercetin is the richest of the flavonoids (Verma et al., 2018). Many studies have been conducted on its many health advantages, which include anticancer, antiviral, antibacterial, anti-inflammatory, and antioxidant qualities. Because of its potent antioxidants, it can prevent oxidative stress, scavenge free radicals, and shield cells from harm. Because quercetin inhibits the synthesis of inflammatory cytokines and enzymes, it has anti-inflammatory characteristics and may be used as a medicinal treatment for a variety of inflammatory disorders. By preventing the growth of cancer cells and triggering apoptosis, it also demonstrates anticancer properties (Aghababaei and Hadidi, 2023).

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one), also known as indigo yellow, is a naturally occurring flavonoid that is a secondary metabolite found in plants and has substantial potential in a variety of biological functions. Kaempferol is a remarkable radical scavenger due to the presence of four hydroxyl substituents and phenyl rings in its chemical structure. In the last several years, a growing body of research has established the importance of kaempferol in controlling intestinal function and reducing intestinal inflammation (Chen et al., 2023).

CONCLUSIONS AND RECOMMENDATIONS

Quercetin and kaempferol are two of the substances in CA that satisfy the criteria for physicochemical and pharmacokinetic predictions made with the pkCSM web toll. In vitro and in vivo testing must be done in order to confirm that the predictions made with the pkCSM web tool are accurate. Additionally, if preparations from this isolation are created in the future, this can be done to enhance the pharmacokinetic characteristics of drugs that don't quite match the requirements.

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