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ADMET Prediction of the Dominant Compound from Mangosteen (*Garcinia mangostana* L.) using pkCSM: A Computational Approach

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A B S T R A C T

Mangosteen (*Garcinia mangostana* L.) is a plant belonging to the Guttiferae family with origins in Southeast Asia. The primary components in mangosteen peel consist of xanthones, particularly α-mangostin, which displays diverse pharmacological effects such as anti-diabetic properties, antioxidant activity, and anti-inflammatory effects. However, due to the insufficient information regarding studies on pharmacokinetics (administration, distribution, metabolism, excretion, and toxicity), the objective of this investigation is to explore pharmacokinetic predictions utilizing the pkCSM web tool. The α-mangostin compound, acquired from PubChem accessible at https://pubchem.ncbi.nlm.nih.gov/, underwent pharmacokinetic analysis using the web tool available at https://biosig.lab.uq.edu.au/pkcsm/prediction. The study findings revealed that the α-mangostin compound, subjected to pharmacokinetic analysis with pkCSM, exhibited limited distribution capability

INTRODUCTION

Mangosteen (*Garcinia mangostana* L.) is a plant that originates from the Guttiferae family and has its roots in Southeast Asia, often cultivated extensively for harvesting purposes (Theapparat et al., 2019). Mangosteen trees can reach heights of 6-25 meters, featuring dense leaves and a rough canopy, with a trunk diameter ranging from 25 to 35 cm, and a bark that varies from brown to black. The tree's structure includes asymmetrical branches that aid in forming a pyramidal crown (Prijayanti et al., 2022). Mangosteen fruit has a dark purple or reddish color, containing soft and juicy white pulp that is edible, and it has a slightly acidic taste (Ibrahim et al., 2014). Mangosteen is renowned as the "Foods of God" due to its unique and distinctive flavor (Ibrahim et al., 2015; Prijayanti et al., 2022).

The use of plants as traditional medicine, including *G. mangostana*, is related to the content of secondary metabolites and their biological activities. For example, the presence of phenolic compounds is often associated with biological activity as antioxidants (Ngawhirunpat et al., 2010). In recent years, the use of *G. mangostana* as a component of traditional medicine has been growing and is believed to have the potential to treat various diseases such as cancer, diabetes mellitus, and heart issues (Silalahi, 2021).

LITERATURE REVIEW

The primary constituents found in mangosteen's pericarp include xanthones, specifically α-mangostin, β-mangostin, γ-mangostin, garcinone E, 8-deoxygartanin, tovophyllin A and B, mangostanol, mangostenin, and mangostenones C, D, and E. The key xanthone derivative, α-mangostin, exhibits various pharmacological effects such as antidiabetic properties, antioxidant activity, and anti-inflammatory effects (Husen et al., 2017; Ansori et al., 2020), in the mangosteen pericarp part there is 121.01 mg/g, while in the mangosteen leaf part there is around 2.10% (Ghasemzadeh et al., 2018; Rahmiyani et al., 2023). Due to a lack of information regarding studies on pharmacokinetics (administration, distribution, metabolism, excretion, and toxicity), the objective of this research is to discuss pharmacokinetic predictions using the web tool pkCSM.

METHODOLOGY

The compound α-mangostin was obtained from the chemical compound library portal of PubChem (https://pubchem.ncbi.nlm.nih.gov/). The comprehensive chemical compound data, which includes Simplified Molecular-Input Line-Entry System (SMILES) data, was retrieved (Jamil and Saputro, 2023). Subsequently, physicochemical and pharmacokinetic analyses were performed using the pkCSM web tool (https://biosig.lab.uq.edu.au/pkcsm/prediction) by inputting the SMILES code for each compound. After entering the SMILES code, users can choose the "ADMET" option on the pkCSM platform and patiently wait for the analysis process to complete. This method provides valuable insights into the absorption, distribution, metabolism, excretion, and toxicity (ADMET)

properties of the mentioned compounds (Muslikh et al., 2023a; Muslikh et al., 2023b).

RESEARCH RESULT AND DISCUSSION

The results of the pharmacokinetic test indicate that α-mangostin exhibits good absorption characteristics based on absorption criteria in the human intestine, but it has less permeability through CaCO2 and high permeability through the skin, as detailed in Table 1. Additionally, concerning distribution parameters, the compound α-mangostin has limited distribution ability, as it only has a CNS permeability value of -1.984, suggesting its potential as a promising drug candidate for targeting the central nervous system (CNS) (Gondokesumo et al., 2024).

Table 1. Prediction of α-mangostin Pharmacokinetics

Parameter	α-mangostin	Indicators
Absorption		
CaCO2 permeability (log Papp in 10^{-6} cm/s)	-0.048	High CaCO2 permeability would value >0.90
Intestinal absorption (human) (% Absorbed)	93.647	Poor absorption, < 30%
Skin permeability (log Kp)	-2.736	Low, log Kp > -2.5
Distribution		
VDSS (human) (log L/kg)	-0.282	Low, log < -0.15 High, log > 0.45
BBB permeability (log BB)	-1.075	Good, logBB > 0.3 Poor, logBB < -1
CNS permeability (log PS)	-1.984	Can penetrate, Log PS > -2 Cannot penetrate, Log PS < -3
Metabolism		
CYP2D6 Substrates	No	Yes/No
CYP3A4 Substrates	Yes	Yes/No
CYP1A2 inhibitors	Yes	Yes/No
CYP2C19 inhibitors	Yes	Yes/No
CYP2C9 inhibitors	Yes	Yes/No
CYP2D6 inhibitors	No	Yes/No
CYP3A4 inhibitors	No	Yes/No
Excretion		
Total clearances	0.43	Higher is better
Renal OCT2 substrates	No	Yes/No
Toxicity		
AMES toxicity	Yes	Yes/No
Max. tolerated dose (human) (log mg/kg/day)	0.061	-
hERG I inhibitors	No	Yes/No
hERG II inhibitors	Yes	Yes/No
Hepatotoxicity	No	Yes/No
Skin Sensitization	No	Yes/No
***T. Pyriformis* toxicity (log ug/L)**	0.325	Toxic, Log > 0.5 ug/L
Minnow toxicity (log mM)	-0.138	The acute toxicity is high, Log < - 0.3

Regarding metabolic parameters, the evaluation of cytochrome P450 inhibition and metabolic indicator produced diverse results. α-Mangostin was identified as a potential substrate for CYP3A4 and showed inhibitory effects on CYP1A2, CYP2C19, and CYP2C9 inhibitors.

In the process of designing drug candidates, toxicity assessment is a crucial parameter. Findings from the toxicity test reveal that α-mangostin exhibits toxicity towards AMES and hERG II inhibitors (Pires et al., 2015; Ma'arif et al., 2021; Muslikh et al., 2022). In the context of excretion analysis, it is noteworthy that α-mangostin shows higher total clearance values. Furthermore, α-mangostin is not categorized as a substrate for renal OCT2, indicating a lack of toxic effects in oral formulations, especially when administered concurrently with a renal OCT2 inhibitor (Pires et al., 2015).

CONCLUSIONS AND RECOMMENDATIONS

The primary compound discovered in Mangosteen (*Garcinia mangostana* L.) is α-mangostin. An in silico pharmacokinetic analysis using the pkCSM suggests that this compound exhibits limited distribution capabilities. Additional studies can be undertaken to formulate drugs utilizing α-mangostin, aiming to improve its distribution characteristics.

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