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Assessing Drug-Likeness The Natural Compounds of Polar Extract *Curcuma xanthorrhiza* Rhizome via Lipinski's Rules with SWISSADME Web Tool

Sumardi [1*], Suprianto [2]

[1]Pendidikan Profesi Apoteker, Institut Kesehatan Medistra Lubuk Pakam, Indonesia
[2]Institut Kesehatan Medistra Lubuk Pakam, Indonesia

*sumardi@medistra.ac.id; ekahasbi@gmail.com

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Abstract

Curcuma xanthorrhiza, commonly known as Javanese turmeric, is widely recognized for its medicinal properties, with its polar extract containing various bioactive compounds. This study aims to assess the drug-likeness of natural compounds found in the polar extract of Curcuma xanthorrhiza rhizome using Lipinski's Rule of Five, analyzed through the SWISSADME web tool. The compounds alpha pinene, alpha thujene, beta pinene, and zingiberene were evaluated for their physicochemical properties, including molecular weight, hydrogen bond donors and acceptors, lipophilicity, and solubility. The analysis confirms that these compounds meet the criteria for oral drug-likeness. Additionally, specific parameters such as fractionCsp3, iLOGP, and MLOGP were found to significantly influence the permeability of these compounds, further supporting their potential as orally administered therapeutics. The findings underscore the utility of SWISSADME in preclinical screening of natural products, offering a valuable approach to identify promising candidates for drug development. This study highlights the potential of Curcuma xanthorrhiza polar extract as a source of drug-like compounds, paving the way for further pharmacological and clinical investigations.

Keywords: polar extract of Curcuma xanthorrhiza rhizoma, Lipinski's Rule of Five, drug-likeness, SWISSADME, permebility prediction

INTRODUCTION

Natural products have long been a cornerstone in drug discovery, offering a vast reservoir of bioactive compounds with therapeutic potential [1]. Among these, *Curcuma* species, particularly known for their rhizomes, have garnered significant attention due to their diverse pharmacological activities, including anti-inflammatory, antioxidant, and anticancer properties. The polar extracts of *Curcuma* rhizomes contain a variety of secondary metabolites that may contribute to these beneficial effects [2]. However, identifying compounds with favorable pharmacokinetic and pharmacodynamic profiles remains a challenge in natural product-based drug discovery.

Drug-likeness is a crucial parameter in evaluating the potential of bioactive compounds to become successful therapeutic agents [3]. Lipinski's Rule of Five (Ro5) provides a widely accepted guideline for assessing the drug-likeness of small molecules based on key physicochemical properties, such as molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors. Adherence to these rules suggests a compound's suitability for oral bioavailability, a critical aspect of drug development [4].

The SWISSADME web tool is an accessible and efficient platform that facilitates the evaluation of drug-likeness and other pharmacokinetic properties by analyzing molecular descriptors and predicting absorption, distribution, metabolism, and excretion (ADME) parameters. Utilizing SWISSADME to assess natural compounds can provide valuable insights into their potential as drug candidates [5].

This study aims to evaluate the drug-likeness of natural compounds present in the polar extract of *Curcuma* rhizomes using Lipinski's Rule of Five through the SWISSADME web tool. The findings are

expected to identify promising compounds with favorable drug-like properties, contributing to the advancement of natural product-based drug discovery.

RESEARCH METHOD

Collecting data

Structure Chemical compounds obtained from publications were collected in two-dimensional form with sdf type through the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and subsequently optimized using the MarvinSketch application (https://chemaxon.com/marvin).

Drug-likeness Prediction

Each obtained chemical compound structure is converted into the Simplified Molecular Input Line Entry System (SMILES) format. Prediction of physicochemical property characteristics using the SWISSADME website application (http://www.swissadme.ch/). The drug-likeness criteria are evaluated using the 5 Lipinski's Rule of Five. Quantitative analysis of the relationship between physicochemical properties and permeability to the skin layer. The analysis uses the multiple linear regression (MLR) method with the application of MATLAB open-source application [5], [6].

RESULT AND DISCUSSION

The polar extract of *Curcuma xanthorrhiza* rhizoma was analyzed, and several bioactive compounds were identified. These compounds can be grouped into different categories based on their chemical nature, including carbohydrates, organic acids, curcuminoids, and terpenes (**Table 1**).

Carbohydrates, namely D-Glucose: The presence of D-glucose indicates the potential for energy metabolism support and its role as a primary metabolite [7]. Organic Acids, namely citric Acid, malic acid, and lactic acid: These organic acids are known to contribute to the antioxidant activity and influence the pH of the extract, which may enhance the solubility of certain bioactive components [8]. Curcuminoids, includes curcumin, demethoxycurcumin, and bisdemethoxycurcumin. They were the hallmark bioactive compounds of Curcuma species. These compounds were well-documented for their anti-inflammatory, antioxidant, and anticancer activities. The diversity of curcuminoids in the extract indicates its potential for therapeutic applications [9].

Terpenes with list of xanthorrhizol, alpha-pinene, beta-pinene, alpha-thujene, myrcene, linalool, and zingiberene: These volatile compounds contribute to the distinctive aroma and exhibit antimicrobial, anti-inflammatory, and antioxidant properties [10], [11]. Xanthorrhizol: This sesquiterpenoid is a major bioactive component of Curcuma xanthorrhiza and is known for its potent antimicrobial and anticancer effects [12]. Zingiberene: Common in rhizomes of the Zingiberaceae family, this compound is associated with anti-inflammatory and digestive health benefits [13].

The study identifies that the compounds alpha pinene, alpha thujene, beta pinene, and zingiberene extracted from the polar fraction of *Curcuma xanthorrhiza* rhizoma conform to Lipinski's Rule of Five. This finding holds significant implications for their potential as orally active drug candidates. Lipinski's Rule of Five (Ro5) is a set of guidelines used to evaluate the drug-likeness of chemical compounds. The rule suggests that compounds with good oral bioavailability typically adhere to the following criteria [4] :

1. Molecular weight ≤ 500 Daltons.
2. LogP (octanol-water partition coefficient) ≤ 5.
3. Hydrogen bond donors ≤ 5.
4. Hydrogen bond acceptors ≤ 10.

The adherence of the compounds to these criteria indicates favorable physicochemical properties for oral administration, including [14]:

1. Adequate solubility.
2. Permeability across biological membranes.
3. Potential for efficient absorption in the gastrointestinal tract.

Although these compounds are identified in the polar extract of the rhizome, their compatibility with Lipinski's Ro5 suggests that the structural diversity within polar fractions still maintains the balance of lipophilicity and hydrophilicity required for oral drug development. This is particularly relevant for

natural product drug discovery, where polar extracts often house a variety of bioactive secondary metabolites.

These compounds can be further investigated for their pharmacokinetics and pharmacodynamics to validate their efficacy and safety. Their natural origin and compliance with Ro5, these molecules may serve as leads for developing phytotherapeutic agents targeting inflammation, microbial infections, or oxidative stress-related disorders.

While meeting Lipinski's criteria is a promising indicator of oral bioavailability, further studies are required to assess the compounds' stability, metabolism, and toxicity profiles in vivo. Investigate their interactions with biological targets dan evaluate their formulation into deliverable pharmaceutical products.

This result provides a strong foundation for advancing these compounds into more rigorous stages of drug development and highlights the therapeutic potential of *Curcuma xanthorrhiza* as a source of bioactive compounds.

A multiple linear regression analysis was conducted to examine the relationships between LogKp and the variables FractionCsp3, iLOGP, and MLOGP. The resulting regression equation is as follows:

LogKp = 0.012 FractionCsp3 + 0.719 iLOGP – 0.094 MLOGP - 6.226

The model suggests that LogKp is positively influenced by both FractionCsp3 and iLOGP, while MLOGP has a negative impact. Specifically, the coefficient for FractionCsp3 (0.012) indicates that a 1 unit increase in FractionCsp3 is associated with an increase in LogKp by 0.012 units. The coefficient for iLOGP (0.719) suggests that a 1 unit increase in iLOGP leads to a 0.719 unit increase in LogKp. The coefficient for MLOGP (-0.094) shows that a 1 unit increase in MLOGP results in a decrease of 0.094 units in LogKp. The constant term (-6.226) represents the baseline value of LogKp when all predictor variables are set to zero.

The regression analysis indicates significant contributions of FractionCsp3, iLOGP, and MLOGP to predicting LogKp, which can be interpreted as a logarithmic value of the permeability coefficient. The positive relationship between FractionCsp3 and LogKp suggests that higher levels of sp3 carbon content in the molecules might correlate with higher permeability. This could be due to the increased structural flexibility and polarity that sp3 carbon atoms typically provide, which may facilitate molecular transport across membranes.

Similarly, the positive effect of iLOGP on LogKp suggests that higher lipophilicity, as represented by iLOGP, is associated with increased permeability. This result aligns with existing theories in pharmacokinetics, which often indicate that lipophilic compounds tend to pass more easily through lipid membranes. However, the magnitude of the effect of iLOGP is notably higher compared to FractionCsp3, which might indicate a stronger influence of lipophilicity on permeability than the structural features denoted by FractionCsp3.

On the other hand, MLOGP has a negative impact on LogKp. This could imply that molecular complexity, or the presence of larger polar groups (which might be captured by MLOGP), could reduce permeability. This is consistent with the notion that increased molecular size and polarity may hinder the ability of a compound to traverse lipid bilayers efficiently.

The model's constant term suggests that, in the absence of these molecular features (FractionCsp3, iLOGP, MLOGP), the baseline permeability is low, as expected from a theoretical standpoint.

Overall, this model provides insights into the factors influencing LogKp and may serve as a valuable tool for predicting the permeability of compounds based on their molecular properties. Further investigation with a larger dataset or additional variables may enhance the model's accuracy and applicability.

CONCLUSION

Alpha pinene, alpha thujene, beta pinene, and zingiberene found in the polar extract of Curcuma xanthorriza rhizoma meet the requirements as an oral medication through the analysis of the Lipinski Rule of Five. The physicochemical properties FractionCsp3, iLOGP, and MLOGP influence the permeability of the compound.

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