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Prediction of Pinostrobin Pharmacokinetics from Temu Kunci (*Boesenbergia rotunda* (L.) Mansf.) Using pkCSM

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A B S T R A C T

Indonesia is a megabiodiversity country with the second-largest abundance of biodiversity in the world. Temu kunci (*Boesenbergia rotunda* (L.)) is a well-known traditional medicinal plant in Indonesia with many nutritional and therapeutic benefits. It is known to have good pharmacological activity, which is due to the content of secondary metabolites commonly known as pinostrobin. However, more scientific data is still needed to justify its increased use, especially regarding its pharmacokinetics and safety. The aim of the research was to predict the pharmacokinetic properties of pinostrobin compounds. The pinostrobin compound was obtained from PubChem, accessible at https://pubchem.ncbi.nlm.nih.gov/, and then pharmacokinetic analysis was carried out using a web tool (https://biosig.lab.uq.edu.au/pkcsm/prediction). The research results show that the pinostrobin compound is a compound that has pharmacokinetic properties, showing that this compound has poor distribution and toxicity capabilities.

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INTRODUCTION

Indonesia, as one of the countries with the world's largest biodiversity, ranks second globally. Positioned geographically between two continents, Asia and Australia, and surrounded by two oceans, the Indian and Pacific Oceans, Indonesia takes pride in being a megabiodiversity nation (Putra et al., 2012; Rosana, 2019). Despite its land area comprising only 1.3% of the total global landmass, Indonesia's biological richness is extensive, encompassing 10% of the world's flowering plant species, 12% of mammals, 16% of reptiles and amphibians, 17% of birds, and 25% of fish (Occhipinti-Ambrogi, 2003; Rosana, 2019).

Boesenbergia rotunda (L.), also known as "temu kunci" in the Indonesian language, is a well-known traditional medicinal plant in Indonesia with numerous nutritional and therapeutic benefits. Belonging to the Zingiberaceae family, this plant holds a significant place in Indonesian culinary and medicinal culture. The rhizome of *B. rotunda* is used as a food ingredient in Indonesia and other countries and plays a crucial role in traditional treatments, including rheumatism, muscle pain, fever, digestive disorders, bloating, and gastric ulcers (Eng-Chong et al., 2012; Saah et al., 2021).

Rhizomes, leaves, and flowers from the Zingiberaceae family are commonly utilized as herbal and food ingredients. Temu kunci has demonstrated significant anticancer, antioxidant, anti-inflammatory, anti-apoptotic, antiulcer, antidiabetic, and antibacterial effects (Saah et al., 2021; Zhang et al., 2023). Key bioactive compounds, such as flavonoids and chalcone derivatives, are responsible for the plant's bioactivity (Wang, 2022; Zhang et al., 2023).

LITERATURE REVIEW

In the context of antioxidant and anti-inflammatory properties, temu kunci has been proven to suppress lipid peroxidation, protein kinase B (Akt), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation while enhancing antioxidant defenses (Wang, 2022; Zhang et al., 2023). Further studies on flavonoids, particularly pinostrobin, pinocembrin, and alpinetin, which are abundant in the rhizome extract of *B. rotunda*, are needed to explore the pharmacodynamic potential and safety of these compounds (Tan et al., 2015; Kanchanapiboon et al., 2020).

This research aims to identify the pharmacokinetic potential and safety of pinostrobin compounds in the *B. rotunda* plant, contributing significantly to a deeper understanding of the health benefits of this herbal plant.

METHODOLOGY

The compound pinostrobin was acquired from the chemical compound library portal of PubChem, accessible at https://pubchem.ncbi.nlm.nih.gov/. The comprehensive chemical compound data, which includes SMILES (Simplecular-Input Line-Entry System) data (Jamil and Saputro, 2023). Subsequently, physicochemical and pharmacokinetic analyses were conducted using the pkCSM web tool (https://biosig.lab.uq.edu.au/pkcsm/prediction) by inputting the SMILES code for each compound. Upon entering the SMILES code, users can select the "ADMET" option on the pkCSM platform and patiently await the completion of the analysis process. This procedure furnishes valuable insights into the adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the aforementioned compounds.

RESULTS AND DISCUSSIONS

Results from pharmacokinetic tests indicate that pinostrobin possesses favorable absorption characteristics, satisfying the criteria for permeability through CaCO2, absorption in the human intestine, and high permeability in the skin, as detailed in Table 1. Additionally, in the distribution parameters section, both compounds exhibited limited distribution ability, as evidenced by values < -0.15. Furthermore, these pharmaceuticals demonstrated the capability to traverse the blood-brain barrier (BBB) and central nervous system (CNS), underscoring their potential as promising drug candidates for targeting the CNS (Gondokesumo et al., 2024).

In terms of metabolic parameters, the evaluation of cytochrome P450 inhibition and metabolism indicators yielded diverse outcomes. The pinostrobin compound was identified as a potential substrate for CYP3A4 and displayed inhibitory effects against CYP1A2 and CYP2C19 inhibitors.

Table 1. Prediction of Pinostrobin Pharmacokinetics

Parameter	Pinostrobin	Indicators
Absorption		
CaCO2 permeability (log Papp in 10^{-6} cm/s)	1.296	High CaCO2 permeability would value >0.90
Intestinal absorption (human) (% Absorbed)	93.762	Poor absorption, if < 30%
Skin permeability (log Kp)	-2.757	Low, if log Kp > -2.5
Distribution		
VDSS (human) (log L/kg)	-0.248	Low, if log < -0.15 High, if log > 0.45
BBB permeability (log BB)	0.085	Good, if logBB > 0.3 Poor, if logBB < -1
CNS permeability (log PS)	-2.072	Can penetrate, if Log PS > -2 Cannot penetrate, if 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	No	Yes/No
CYP2D6 inhibitors	No	Yes/No
CYP3A4 inhibitors	No	Yes/No
Excretion		
Total clearances	0.236	Higher is better
Renal OCT2 substrates	No	Yes/No
Toxicity		
AMES toxicity	Yes	Yes/No
Max. tolerated dose (human) (log mg/kg/day)	0.260	-
hERG I inhibitors	No	Yes/No
hERG II inhibitors	No	Yes/No
Hepatotoxicity	No	Yes/No
Skin Sensitization	No	Yes/No
***T. Pyriformis* toxicity (log ug/L)**	0.681	Toxic, if Log > 0.5 ug/L
Minnow toxicity (log mM)	0.492	The acute toxicity is high, if Log < -0.3

In the process of designing drug candidates, assessing toxicity is a crucial parameter. Findings from toxicity tests reveal that pinostrobin demonstrates toxicity against AMES and T. Pyriformis toxicity (Pires et al., 2015). In the context of excretion analysis, it is noteworthy that, pinostrobin exhibits a higher total clearance value. Moreover, pinostrobin is not categorized as a Renal OCT2 substrate, indicating its lack of toxic effects in oral formulations, especially when co-administered with renal OCT2 inhibitors (Pires et al., 2015).

CONCLUSIONS AND RECOMMENDATIONS

Pinostrobin is a compound found in *Boesenbergia rotunda*. Pharmacokinetic analysis using in silico tests based on pkCSM results shows that this compound has poor distribution and toxicity capabilities. Further research can be carried out to create drug formulations based on pinostrobin which can improve its distribution properties and toxicity.

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