MEDFARM: Jurnal Farmasi dan Kesehatan, Vol. 15, No. 1, 2026, Page 186-199
e-ISSN : 2715-9957
p-ISSN: 2354-8487

Molecular Docking Study of *Pongamia pinnata* Phytochemicals as Phosphodiesterase-4 Inhibitors for Atopic Dermatitis

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ABSTRACT

Atopic dermatitis is a chronic inflammatory skin disease characterized by recurrent itching, eczematous lesions, and associated with significant impairment in quality of life. Current therapies for AD, including corticosteroids and calcineurin inhibitors, are often associated with adverse effects, highlighting the need for safer alternatives. *Pongamia pinnata* is widely used in traditional medicine and has demonstrated anti-inflammatory and antioxidant properties. Therefore, this study aimed to explore the potential of *P. pinnata* phytochemicals as phosphodiesterase-4 inhibitors for atopic dermatitis through molecular docking analysis. Molecular docking analysis was conducted against phosphodiesterase-4 to evaluate their binding affinities and key amino acid residues compared to the native ligand and roflumilast as the reference drug. Subsequently, Lipinski's Rule of Five was applied to assess the oral drug-likeness properties of the selected compounds. Karanjachromene exhibited the highest binding affinity toward PDE4 (ΔG = −8.17 kcal/mol), exceeding both the reference drug roflumilast (ΔG = −6.47 kcal/mol) and the native ligand (ΔG = −7.81 kcal/mol). Interaction analysis demonstrated that karanjachromene shared several key amino acid residues with the native ligand, indicating similar binding interactions with phosphodiesterase-4. In addition, karanjachromene fulfilled Lipinski's Rule of Five and favorable ADMET properties, suggesting oral administration potential. However, further in vitro and in vivo evaluations are required to validate its pharmacokinetics, bioavailability, and pharmacological activity against phosphodiesterase-4.

Keywords: Atopic dermatitis, docking, karanjachromene, phosphodiesterase-4, *P. pinnata*

Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder characterized by persistent pruritus and eczematous lesions (Gołuchowska et al., 2025). This condition affects individuals across all age groups, with an estimated prevalence ranging from 2% to 22% among children worldwide, particularly in industrialized countries and low-income regions (Pinto et al., 2022). Multifactorial interactions among skin barrier dysfunction, environmental exposure, immune dysregulation, and alterations in the skin microbiome involved in the pathogenesis of AD. In addition, the clinical heterogeneity of AD has been associated with distinct molecular signatures that may contribute to the development of targeted therapeutic strategies in the future (Meledathu et al., 2025).

According to Global Burden of Disease, AD ranks as the 15th most prevalent nonfatal skin disease afflicting both males and females (Khan et al., 2022). Persistent itching and sleep disturbances caused by AD can significantly impair Quality of Life (QoL). Furthermore, the chronic and visible manifestations of AD are associated with psychosocial and neuropsychiatric conditions, including social withdrawal, depression, insomnia, and compulsive scratching behaviors (Courtney & Su, 2024). AD also continues to impose considerable social and economic burdens due to reduced productivity and high treatment costs (Yang et al., 2019).

he primary objective of AD management is to control symptoms and prevent recurrent flare-ups. Treatment selection is generally based on disease severity and clinical manifestations while considering patient preferences, treatment expenses, and the risk of adverse drug reactions (Jeskey et al., 2024). Current treatment options for atopic dermatitis are limited to topical emollients, corticosteroids (TCS), calcineurin inhibitors (TCI) and immunosuppressive agents. However, prolonged use of TCS may lead to adverse effects such as petechiae, telangiectasia, skin atrophy, and skin thinning (Tang et al., 2022). Similarly, long-term administration of TCI has been associated with local irritation and burning sensations (Shin et al., 2021). Phosphodiesterase-4 (PDE4) inhibitors have emerged as non-steroidal alternatives for AD treatment with relatively tolerable side effects (Pinto et al., 2022). Nevertheless, crisaborole, an FDA-approved PDE4 inhibitor, remains financially inaccessible for many patients (Frazier & Bhardwaj, 2020).

These limitations have encouraged the exploration of safer therapeutic alternatives. Among natural resources, *P. pinnata* is widely used in traditional medicine, particularly in the Indian medicine systems of Ayurveda and Siddha. *P. pinnata* exhibited several pharmacological activities, such as antioxidant, anti-inflammatory, antimicrobial, antifungal, anticancer, antidiabetic, and neuroprotection (Jeelani et al., 2025). Previous studies have demonstrated the anti-inflammatory and antioxidant potential of *P. pinnata.* Ethanolic extracts of *P. pinnata* seeds exhibited significant dose-dependent antioxidant activity in the DPPH assay, inhibitory activity increasing from 10.74% at 100 µg to 74.9% at 500 µg. In the albumin denaturation assay, the extract also exhibited considerable anti-inflammatory activity, reaching 68% inhibition at 500 µg (Yasothkumar et al., 2023). These findings suggest that phytochemicals of *P. pinnata* have strong potential for the management of inflammatory disorders.

However, the potential effects of *P. pinnata* phytochemicals on the pathogenesis of AD have not been extensively investigated. In vitro and in vivo screening methods require substantial financial resources and considerable time. Therefore, in silico approaches have become increasingly important as preliminary tools in drug discovery, as they can accelerate the identification of promising drug candidates while reducing resource consumption (Roney & Mohd Aluwi, 2024). This study aimed to investigate the potential of *P. pinnata* phytochemicals as PDE4 inhibitors for atopic dermatitis through molecular docking analysis.

Methodology

Protein and ligand preparation

The 3D structure of PDE4 (ID: 8WDN) was obtained from PDB Database (https://www.rcsb.org/) (Berman et al., 2000). Protein preparation using AutoDock Tools 1.5.6 includes removal of water, ions, and ligand, adding polar hydrogen, assigned Kollman Charges and Compute Gasteiger (Hasyim et al., 2025).

3D structure of *P. pinnata* phytochemicals were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in the SDF format (*.sdf) (Gayathri et al., 2024). Geometry optimization was carried out using Avogadro 2.0.0 with the MFF94 method and then converted into PDB files (*.pdb) (Hanwell et al., 2012). Roflumilast was selected as the reference drug due to its established activity as a PDE4 inhibitor and clinically relevant to atopic dermatitis treatment (Simpson et al., 2024).

Docking procedure

The protein structure was validated in AutoDock Tools 1.5.6 which generated RMSD value. The method was considered valid when the RMSD values were <2 Å (Saputro et al., 2023). The optimized ligands were then docked with the target protein using AutoDock Tools 1.5.6 (Morris et al., 2009).

Analysis of interaction

Visualization of the interaction between ligand and protein was performed by Biovia Discovery Studio 2021. The visualization provided a view of interaction between each chemical functional group of the ligand interacting with every amino acid residue of the target protein.

Lipinski's Rules of Five and ADMET Predictions

The SMILES code of *P. pinnata* phytochemicals were retrieved from PubChem (www.pubchem.ncbi.nlm.nih.gov) (Kim et al., 2025). Subsequently, the compounds were further evaluated using Lipinski's Rules of Five (RO5) through pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) (Pires et al., 2015). The assessed parameters included molecular weight (≤ 500 Daltons) lipophilicity (Log P ≤ 5), hydrogen bond donors (HBD ≤ 5), hydrogen bond acceptors (HBA ≤ 10) (Illian et al., 2022). Following molecular docking analysis, the compound demonstrating the most favorable binding free energy, interaction profile, and compliance with RO5 was selected for further absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile prediction to provide broader insight into its potential.

Results and Discussion

Method validation

Method validation has been conducted to determine the size and coordinates of the grid box, which will be used for docking subsequently. The specification of the methods used in the validation showed in **Table 1**.

Table 1. Grid box size and coordinate

PDB ID	Native Ligand	Grid Box Size	Grid Box Center			RMSD (Å)	ΔG
			x	y	z		
8WDN	71-b	x: 22 y: 28 z: 28	26.896	77.245	25.465	0.60	-7.81

RMSD: *Root Mean Square Deviation*; ΔG: binding free energy (kcal/mol).

The RMSD values obtained from redocking of receptor with native ligand is below 2 Å, indicates that the method employed in docking for receptor is valid (Khachatryan et al., 2024). This is consistent with the illustration in **Figure 1**, which shows no significant conformational difference between before and after redocking.

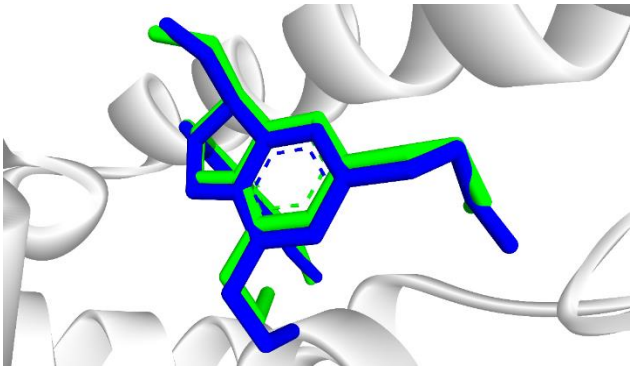

Figure 1. Overlapping redocking position (green) with native ligand (blue)

Docking and analysis of interactions

Phosphodiesterase-4 (PDE4) works by converting the cellular secondary messenger cyclic adenosine monophosphate (cAMP) into 5'-adenosine monophosphate, which plays a role in pro-inflammatory cytokine responses expression such as interleukin (IL)-4, IL-13, and IL-31. Inhibition of PDE activity can reduce the expression of pro-inflammatory cytokines by increasing intracellular cAMP (Yang et al., 2019). Therefore, PDE4 has become a promising therapeutic target for atopic dermatitis.

Several parameters were obtained from the molecular docking analysis, including binding energy values (ΔG, kcal/mol), the number of hydrogen bonds and hydrophobic interactions, as well as the amino acid residues. Lower binding free energy values indicate stronger binding affinity (Shah et al., 2024). Among the tested compounds, karanjachromene exhibited the lowest binding free energy value (−8.17 kcal/mol), followed by β-sitosterol (−8.05 kcal/mol), as shown in **Table 2**. Notably, both compounds showed lower binding free energy values than the native ligand and roflumilast as the reference drug (−7.81 kcal/mol and −6,47 kcal/mol, respectively).

In addition, several tested compounds demonstrated lower binding free energy values than roflumilast, although their binding affinities were still less favorable than the native ligand. These compounds included karanjin, kanjone, pongapin, pongachalcone I, glabrachromene II, stigmasterol, and kanugin with binding free energy −7.76 kcal/mol, −7.02 kcal/mol, −7.44 kcal/mol, −7.01 kcal/mol, −6.89 kcal/mol, −7.11 kcal/mol, and −7.13 kcal/mol, respectively. These findings indicate that *P. pinnata* phytochemicals may possess promising inhibitory potential against PDE4. However, molecular docking results only provide preliminary insights into ligand–receptor interactions and binding affinity predictions. Therefore, further in vitro and in vivo studies are necessary to validate the biological activity and therapeutic potential of these compounds.

Previous studies have explored various plant-derived compounds as potential PDE4 inhibitors, including curcumin from *C. longa* (−11.03 ± 0.25 kcal/mol), 6-gingerol from ginger (−6.99 ± 0.39 kcal/mol), capsaicin from chilli pepper (−5.24 ± 0.35 kcal/mol), and resveratrol (−4.59 ±0.41 kcal/mol), based on molecular dynamics simulations (Furlan & Bren, 2021). In another study employing AutoDock Vina, compounds isolated from *Millettia dielsiana* showed docking scores ranging from −5.8 to −12.12 kcal/mol, with compound D50 (5,7,4′-trihydroxyisoflavone7-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside) identified as the most favorable binding affinity toward PDE4 (Le et al., 2023). Although direct numerical comparison should be interpreted with caution due to differences in computational methods and PDE4 crystal structures used, the docking score of karanjachromene (−8.17 kcal/mol) is within the range reported for natural PDE4 inhibitors, supporting its potential interaction with the PDE4 active site.

Table 2. Docking results

Compounds	ΔG (kcal/mol)	Amino Acid Residues	
		Hydrogen Bonds	Hydrophobic Interactions
Native Ligand	−7.81	His160, Cys358, Gln369, Pro356, Phe340	Ile336, Phe372, Met357, Tyr329, Phe340
Roflumilast	−6.47	Gln369, Ser368	Phe372, Phe340, Ile336, Met357, Tyr159, His160
Karanjin	−7.76	Gln369	Ile336, Met337, Phe340, Phe372, Tyr159, Met273, Met357
Kanjone	−7.02	His160	Ile336, Met337, Phe340, Phe372, Tyr159, Met273, His160, Met357
Pongapin	−7.44	Gln369, Asn321	Met357. Phe372, Phe340, Met273, His160, Ile336, Met357
Karanjachromene	−8.17	His160, Gln369	Ile336, Met337, Phe340, Phe372, Tyr159, Met273, His160, Met357
Isopongachromene	−2.57	Asn321	Ile336, Phe340, Tyr159, His160, Trp332

Pongachalcone I	−7.01	Gln369, Asn321	His160, Tyr159, Phe372, Phe340, Met357, Ile336
Glabrachalcone	−5.10	Ser208, Gly206, Gln343	Met357, Met337, Phe372, Phe340, Ile336, Cys358, His160
Glabrachromene II	−6.89	Gln369	Ile336, Phe340, Phe372, Met357, Cys358
β-sitosterol	−8.05	Val365	Phe372, Ile336, Met337, Met357, Met273, His160, His204, Phe340
Stigmasterol	−7.11	Val365	Phe372, His160, Met357, Met273, Ile336, Met337, His204, Phe340
Stigmasteryl acetate	−3.60		Ile336, Met357, Tyr159, His160, Phe340, Phe372
β-sitosteryl acetate	−3.97		Phe340, Ile336, Met357, Leu319, Cys358, Tyr159, Phe372
Kanugin	−7.13	Gln369, Gly206, Gln343	His160, Ile336, Phe372, Tyr159, Met357, Phe340
Glabrin	−2.60	Gln369, Asn321	

ΔG: binding free energy.

Similarities in amino acid residues between native ligand–receptor and test ligand–receptor interactions may suggest the involvement of comparable binding mechanisms contributing to the desired pharmacological activity (Saputro et al., 2023). The key amino acid residues identified include His160, which is involved in the metal-binding pocket (M-pocket) that accommodates metal ions such as Zn^{2+} and Mg^{2+}. Interactions within the solvent-accessible pocket (S-pocket) are characterized by Pro356 as a key residue. Meanwhile, the hydrophobic pocket (Q-pocket) comprises invariant residues, including Gln369, Phe372, Phe340, and Ile336, which are critical for maintaining binding affinity (Gu et al., 2024). Based on **Figure 2,** karanjachromene demonstrated favorable interactions with key amino acid residues similar to those of the native ligand. Karanjachromene interacted with His160 and Gln369 through hydrogen bonds, while hydrophobic interactions were identified with Met357, Ile336, and Phe372. Similar interactions were also observed in roflumilast as the reference drug, which interacted with Gln369 through hydrogen bonding and with Phe372, Ile336, and Met357 through hydrophobic interactions.

Karanjachromene is a pyranoflavonoid characterized by a flavone core fused with a 2,2-dimethylpyran ring across the C-7 and C-8 positions of the flavonoid A-ring, while the flavonoid C-ring bears a methoxy substituent at the C-3 position (Arshad et al., 2013). As shown in **Figure 2,** the oxygen atom within the fused dimethylpyran ring, together with the methoxy substituent at the C-3 position, was predicted to facilitate hydrogen bond interactions with His160 and Gln369, respectively. The hydrophobic interactions observed with Phe372 and Ile336 may be attributed to the aromatic flavonoid scaffold of karanjachromene, which appears to facilitate π–alkyl and other nonpolar contacts within the PDE4 binding pocket. The S-pocket interaction was not observed in karanjachromene. In the native ligand, this interaction is facilitated by the dihydrobenzofuran ring, which extends toward the S-pocket and supports interaction with Pro356 (Gu et al., 2024).

MEDFARM: Jurnal Farmasi dan Kesehatan, Vol. 15, No. 1, 2026, Page 186-199
e-ISSN : 2715-9957
p-ISSN: 2354-8487

Based on molecular docking result shown in **Table 2,** glabrin exhibited the highest binding free energy (-2.60 kcal/mol) among all compounds, indicating unfavorable binding affinity towards PDE4. **Figure 2** shows the 2D interaction profile of glabrin with PDE4. Although glabrin engages the Q-pocket residue Gln369 through a conventional hydrogen bond, this interaction alone appears insufficient to stabilize the complex. This likely reflects to structural incompatibility, which limits the formation of additional hydrogen bonds and hydrophobic interactions for optimal ligand–protein binding.

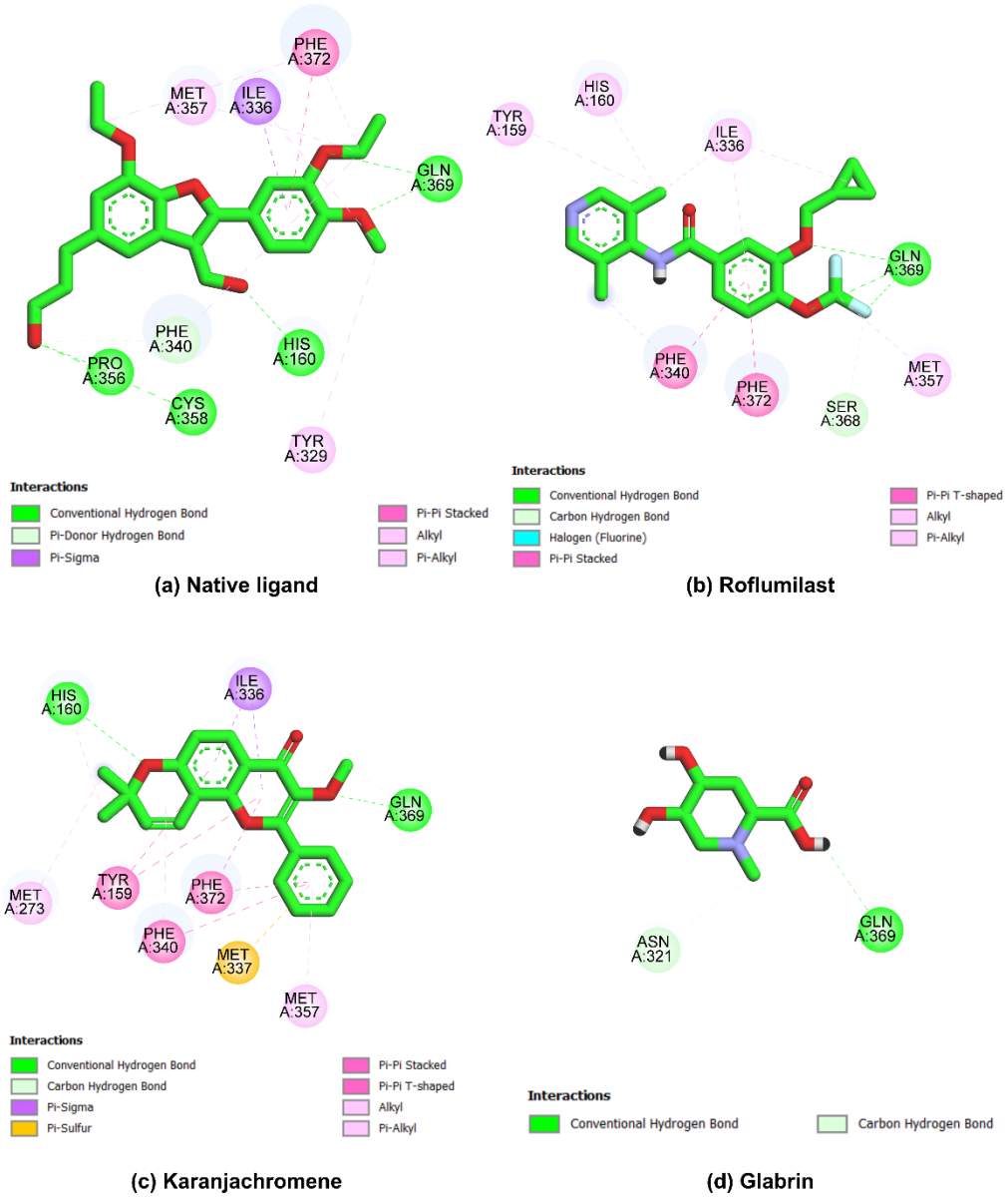

Figure 2. 2D Visualization of interaction

Lipinski's Rules of Five

The physicochemical properties of drug candidates can influence their pharmacokinetic profile and bioavailability in pharmaceutical applications (Andrýsková et al., 2024). Unfavorable pharmacokinetic characteristics of a drug candidate, as well as its toxic properties, can significantly reduce effectiveness and increase costs (Rammali et al., 2024). Therefore, predicting the pharmacokinetic profile and toxicity of compounds can serve as an effective approach to screening drug candidates with the greatest potential.

Table 3. RO5 of *P. pinnata* phytochemicals

Compounds	Pubchem ID	MW (g/mol)	Log P	HBA	HBD
Karanjin	100633	292.29	4.21	4	0
Kanjone	10957726	306.27	3.93	5	0
Pongapin	3083586	336.30	3.94	6	0
Karanjachromene	14033983	334.37	4.65	4	0
Isopongachromene	44257584	378.38	4.38	6	0
Pongachalcone I	11056805	336.39	4.48	4	1
Glabrachalcone	42607548	396.44	4.50	6	1
Glabrachromene II	6442711	350.37	4.20	5	1
β-sitosterol	222284	414.72	8.02	1	1
Stigmasterol	5280794	412.70	7.80	1	1
Stigmasteryl acetate	6437330	454.74	8.37	2	0
β-sitosteryl acetate	5354503	456.76	8.60	2	0
Kanugin	12305452	356.33	3.21	7	0
Glabrin	161850	175.18	-1.50	4	3

MW: Molecular weight; Log P: Partition coefficient; HBA: *Hydrogen bond acceptor*; HBD: *Hydrogen bond donor*.

Lipinski's Rule of Five (RO5) is widely applied to assess the drug-likeness of compounds intended for oral administration, which is generally preferred due to its non-invasive and safer characteristic compared to intravenous or subcutaneous routes (Asano et al., 2024). According to **Table 3,** karanjachromene fulfilled the important drug-likeness parameters according to Lipinski's Rule of Five, indicating favorable physicochemical characteristics (Zafar et al., 2023). Meanwhile, β-sitosterol exhibited one violation, with a Log P value of 8.02, exceeding the recommended criterion (Log P ≤ 5). This indicates markedly high lipophilicity, which may limit its drug-likeness and oral bioavailability. However, further in vitro and in vivo studies are necessary to validate the bioavailability and membrane permeability of these compounds. In addition, multiparameter scoring approaches may provide a more comprehensive estimation of overall drug-likeness than individual physicochemical cutoff values alone (Di et al., 2020).

ADMET Prediction Results

Given that karanjachromene demonstrated the most favorable docking profile and complied with Lipinski's Rule of Five, ADMET prediction was carried out to

further evaluate its pharmacokinetic properties and drug-likeness potential. The absorption, distribution, metabolism, excretion, and toxicity profile prediction of karanjachromene are summarized in **Table 4.**

Table 4. ADMET Prediction Profile of Karanjachromene

Category	Parameter	Value	Interpretation
Absorption	Water solubility (log mol/L)	-4.644	For enteral drugs, lipid-soluble are less well absorbed than wate-soluble ones (Pires et al., 2015).
	Caco-2 permeability (log Papp in 10^{-6} cm/s)	1.414	1×10^{-6} cm/s up to 7×10^{-6} cm/s is classified as medium permeability (Wang et al., 2025).
	HIA (%)	97.591	70 to 100% indicating effective absorption (Linani et al., 2024).
	Skin permeability (log Kp)	-2.591	A value more than -2.5 cm/h considered to have relatively poor skin permeability (Muharrami et al., 2024).
Distribution	Human VDss (log L/kg)	0.283	A value less than 0.45 indicate the higher distribution in plasma (Vijayakumar et al., 2020).
	BBB permeability (log BBB)	0.226	A value less than 0.3 indicate moderate BBB permeability (Muharrami et al., 2024).
	CNS permeability (log PS)	-1.492	A value below -2 indicating limited CNS permeability (Fachriyah et al., 2026).
Metabolism	CYP2D6 substrate	No	Substrate or inhibitory activity toward CYP enzymes suggests potential involvement in formation of toxic metabolites and undesirable drug–drug interactions (Prayogi et al., 2025).
	CYP3A4 substrate	Yes	
	CYP1A2 inhibitor	Yes	
	CYP2C19 inhibitor	Yes	
	CYP2C9 inhibitor	Yes	
	CYP2D6 inhibitor	No	
	CYP3A4 inhibitor	No	
Excretion	Total Clearance (log mL/min/kg)	0.205	Relates to bioavailability and needed to determine the dosage amount to achieve steady-state concentrations (Muharrami et al., 2024).
	Renal OCT2 substrates	Yes	OCT2 substrates may potentially produce side interactions (Muharrami et al., 2024).
Toxicity	AMES toxicity	No	Suggesting a low risk of inducing genetic mutations (Muharrami et al., 2024).
	Human max. tolerated dose (log mg/kg/day)	0.069	Value less than or equal to 0.477 is considered low (Pires et al., 2015).
	hERG I inhibitor	No	

Category	Parameter	Value	Interpretation
	hERG II inhibitor	No	Suggesting a lack of cardiotoxicity and low risk inducing cardiac arrhythmia (Fachriyah et al., 2026).
	LD_{50} oral rat acute toxicity (mol/kg)	2.426	The dose of a compound required to cause death in 50% of the tested animal population (Muharrami et al., 2024).
	Oral rat chronic toxicity (LOAEL) (mg/kg_bw/day)	1.618	Higher LOAEL values suggest a lower risk of adverse effects, whereas lower values indicate greater toxicity concern (Pires et al., 2015).
	Hepatotoxicity	No	Indicating no adverse effect on liver function (Fachriyah et al., 2026).
	Skin sensitization	No	Suggesting a lack of potential for skin sensitization (Fachriyah et al., 2026).
	T. Pyriformis toxicity (IGC_{50} in log μg/L)	0.464	A value more than -0.5 is considered toxic (Pires et al., 2015).
	Minnow toxicity (LC_{50} in log mM)	-0.68	A value below -0.3 is regarded as high acute toxicity (Pires et al., 2015).

HIA: Human intestinal absorption; VDss: Volume of distribution at steady state; BBB: Blood brain barrier

Although studies specifically investigating karanjachromene remain limited, flavonoid and chromene derivatives have been widely recognized for their anti-inflammatory and other pharmacological activities. According to **Table 4,** karanjachromene may possess favorable oral pharmacokinetic properties by its high intestinal absorption and moderate Caco2 permeability. Distribution analysis indicated a moderate VDss value, suggesting balanced distribution between plasma and tissues. Moreover, the predicted BBB permeability value suggests limited penetration across the blood–brain barrier, which may reduce the likelihood of undesirable central nervous system exposure. Although karanjachromene was predicted to interact with several CYP isoforms, potentially contributing to CYP-mediated metabolism and drug–drug interactions, the absence of Ames mutagenicity, hepatotoxicity, and hERG inhibition supports a favorable safety profile. Notably, the predicted skin permeability and the absence of predicted skin sensitization potential suggest that karanjachromene may be capable for topical delivery. Nevertheless, these findings are based on computational predictions and require further experimental validation.

Conclusion

Molecular docking studies of *P. pinnata* phytochemicals identified that karanjachromene demonstrated notable computational profiles, including favorable binding interactions within the PDE4 binding pocket, compliance with Lipinski's Rules of Five, and favorable ADMET profiles, suggesting potential as a candidate

compound with PDE4 inhibitory activity with oral administration potential. However, further in vitro and in vivo evaluations are required to validate pharmacokinetics, bioavailability, and pharmacological activity against PDE4.

Declaration of Competing Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgement

This study is funded by the "Direktorat Penelitian dan Pengabdian kepada Masyarakat, Direktorat Jenderal Riset dan Pengembangan, Kementerian Pendidikan Tinggi, Sains, dan Teknologi, Republik Indonesia" through the research scheme Penelitian Dosen Pemula (PDP) 2025, under contract number 018/C3/DT.05.00/PL/2025, sub-number 1483ah/IT9.2.1/PT.01.03/2025.

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