MOLECULAR DOCKING AND ADMET ANALYSIS OF METABOLITE-PROFILING-DERIVED COMPOUNDS FROM 70% ETHANOL EXTRACT OF UVARIA RUFA ROOTS AS CANDIDATES FOR ERECTILE DYSFUNCTION THERAPY

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Abstrak

Erectile dysfunction (ED) requires safer long-term therapeutic alternatives to conventional PDE5 inhibitors. Uvaria rufa Blume (radiks lelak), traditionally used as an aphrodisiac, contains diverse metabolites with potential activity on ED-related pathways. This study focused on evaluating the binding affinity and pharmacokinetic feasibility of metabolites from the 70% ethanol extract of U. rufa roots against the PDE5A receptor using a targeted in silico approach. Molecular docking was performed using Molegro Virtual Docker to assess ligand–receptor interactions. Two metabolites (5-({4-[Butyl(hexyl)amino]-6-(pentylamino)-1,3,5-triazin-2-yl}amino)-2-methyl-1H-isoindole-1,3(2H)-dione) and 5,7-dimethoxy-3',4'-diprenyloxyisoflavone showed the strongest affinity toward PDE5A, exhibiting favorable Moldock and rerank scores and forming key interactions within the active site comparable to the reference ligand. ADMET predictions using pkCSM revealed that both compounds possessed good absorption characteristics, acceptable distribution parameters, and low predicted toxicity. These findings suggest that the two top-ranking metabolites of U. rufa have promising potential as natural PDE5A inhibitors and warrant further experimental validation to explore their efficacy as ED therapeutic candidates..

Keywords: *Erectile dysfunction; Uvaria rufa Blume; PDE5A; Rerank Score; ADMET*

Introduction

Erectile dysfunction (ED) is a common male sexual disorder defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. This condition not only affects physical health but also has significant psychological and relational consequences, particularly within marital relationships (Amrin, Tendean and Turalaki, 2021). Globally, the

prevalence of ED varies widely, ranging from approximately 3% to 76.5%, and its incidence increases with age, although it can also occur in men younger than 40 years. In Indonesia, epidemiological studies report that the prevalence of moderate to severe ED is approximately 4%, while other population-based studies have shown prevalence rates of up to 36.5% among men aged 20–80 years. The etiology of ED is multifactorial, involving vascular, neurogenic, hormonal, structural, and psychogenic factors, as well as adverse effects of certain medications such as anticholinergics, psychotropic drugs, diuretics, and β-blockers (Ikram et al., 2022).

The physiological mechanism of penile erection is primarily regulated by vascular and neurochemical signaling pathways involving nitric oxide (NO). During sexual stimulation, NO released from non-adrenergic non-cholinergic neurons activates guanylate cyclase, which catalyzes the conversion of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). Increased intracellular cGMP levels induce relaxation of smooth muscle cells in the corpus cavernosum, thereby promoting increased blood flow and penile erection. However, the enzyme phosphodiesterase type 5 (PDE5) hydrolyzes cGMP into inactive guanosine monophosphate (GMP), leading to the termination of the erectile response. Consequently, inhibition of PDE5 has become a well-established pharmacological strategy in ED therapy. Currently available PDE5 inhibitors such as sildenafil, tadalafil, and vardenafil are widely used as first-line treatments. Despite their effectiveness, these drugs may produce adverse effects including headache, flushing, nasal congestion, dyspepsia, and visual disturbances, and may interact with other medications, thereby limiting their long-term therapeutic use (Dahril, 2017).

Natural products represent an important source of structurally diverse bioactive compounds for drug discovery. Countries with high biodiversity, such as Indonesia, possess thousands of plant species with potential medicinal value (Tenggara and Yassir, 2018). One plant that has attracted ethnomedicinal attention is *Uvaria rufa* Blume (family Annonaceae), locally known as lelak. This climbing plant grows in dry monsoon forests, particularly in eastern Indonesia, and its roots have traditionally been consumed as a decoction by local communities in East Nusa Tenggara to treat male sexual dysfunction. Previous metabolite-profiling studies of the 70% ethanolic root extract of *U. rufa* have identified numerous secondary metabolites that may contribute to its pharmacological activity. However, despite its traditional use as an aphrodisiac, scientific investigations exploring the molecular mechanisms and therapeutic potential of these metabolites in ED treatment remain limited (Taek et al., 2024).

Advances in computational drug discovery have enabled rapid screening of bioactive compounds and prediction of their pharmacological properties in the early stages of drug development. In silico approaches such as molecular docking allow the evaluation of ligand–receptor interactions and binding affinity toward specific biological targets, while ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction provides insight into pharmacokinetic behavior and safety profiles of candidate compounds. These computational strategies can significantly accelerate the identification of promising drug candidates derived from natural products. Therefore, the objective of this study was to identify metabolites from the ethanolic root extract of *Uvaria rufa* that may act as PDE5A inhibitors by evaluating binding affinity, ligand–receptor interactions, and predicted pharmacokinetic and toxicity profiles (Isyrafi, 2024).

Methods

Ligand Preparation

Chemical compounds identified from the metabolite profiling of the 70% ethanol extract of *Uvaria rufa* roots were used as ligands in this study (Taek *et al.,* 2025). The two-dimensional structures of the compounds were drawn using ChemDraw within the ChemOffice environment. The 2D structures were converted into three-dimensional conformations and subjected to geometry optimization to obtain energetically stable molecular configurations. The optimized ligand structures were saved in compatible file formats for docking simulations (Imran *et al*., 2025).

Receptor Validation

Phosphodiesterase-5A (PDE5A) was selected as the receptor target in this study because it plays a crucial role in the pathophysiology of erectile dysfunction by hydrolyzing cyclic guanosine monophosphate (cGMP), thereby reducing smooth muscle relaxation and impairing penile erection. PDE5 is highly expressed in penile smooth muscle and is involved in regulating the NO/cGMP signaling pathway. Inhibition of PDE5 increases intracellular cGMP levels, promotes smooth muscle relaxation, enhances penile blood flow, and improves erectile function, making PDE5 a major therapeutic target for erectile dysfunction treatment (Tienforti *et al*., 2025). The reliability of the docking protocol was validated using a re-docking procedure. The native ligand originally present in the receptor crystal structure was extracted and subsequently re-docked into the receptor binding pocket using Molegro Virtual Docker. The accuracy of the docking method was evaluated by calculating the Root Mean Square Deviation (RMSD) between the predicted ligand pose and the experimentally determined crystallographic pose. An RMSD value below 2.0 Å was considered acceptable, indicating that the docking protocol could reliably reproduce the native ligand binding orientation within the active site. (Putra *et al*., 2025).

Molecular Docking Simulation

Molecular docking simulations were carried out using Molegro Virtual Docker to evaluate the interaction between the ligands and the selected target proteins. Validation of the docking protocol was conducted through re-docking of the native ligand into the active site of the target protein (Aghahosseini *et al*., 2024). The docking method was considered valid when the RMSD value was less than 2.0 Å, indicating acceptable accuracy and reproducibility of the docking pose. The docking process was performed by positioning the ligands within the active binding site of the receptor, followed by calculation of the binding affinity and interaction energy. The docking results were evaluated based on the Moldock score expressed in kcal/mol, hydrogen bond interactions, and the involvement of amino acid residues within the binding pocket. Compounds exhibiting lower Moldock score values (kcal/mol) were considered to possess stronger binding affinity toward the target protein. Visualization of ligand–receptor interactions was conducted to identify the types of interactions, including hydrogen bonding and hydrophobic interactions, which may contribute to the stability of the complex (Putra et al., 2025). Furthermore, molecular dynamics simulations were performed for 50 ns with frame recording every 50 ps, resulting in 1000 frames that were subsequently used to analyze the structural stability and protein–ligand.

ADMET Prediction Analysis

The pharmacokinetic and toxicity profiles of the best-performing compounds from the molecular docking analysis were further evaluated through ADMET prediction. The chemical structures of the selected compounds were converted into Simplified Molecular Input Line Entry System (SMILES) format. The SMILES data were then analyzed using the pkCSM online platform (version 1.0). The pkCSM platform has been validated for predicting pharmacokinetic and toxicity (Hidayah *et al*., 2024 ; Pires et al., 2015). The ADMET parameters assessed included absorption, distribution, metabolism, excretion, and toxicity properties. Absorption parameters consisted of Caco-2 permeability and aqueous solubility (Log S). Distribution parameters included the volume of distribution (Vd) and blood– brain barrier permeability (Log BB). Metabolic properties were evaluated based on potential interactions with cytochrome P450 enzymes, particularly CYP inhibition. Excretion parameters included total clearance (Cl), elimination rate constant (k), and half-life (t½). Toxicity predictions included the median lethal dose (LD50) and potential hepatotoxicity (Sulistyowaty *et al*., 2025).

Results and Discussion

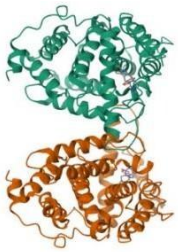
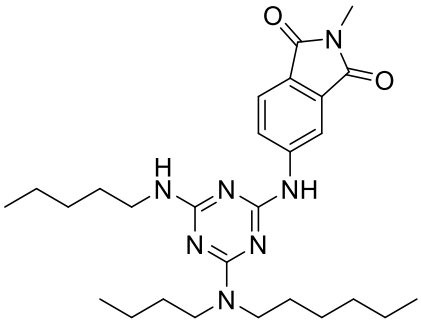
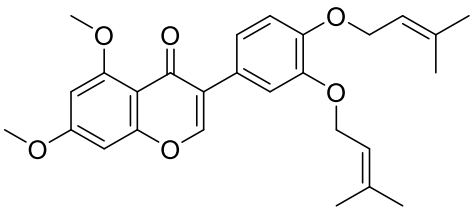
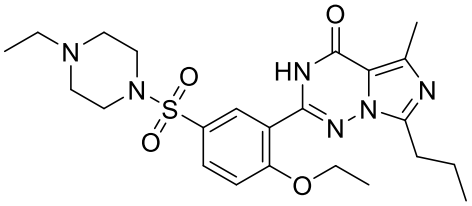
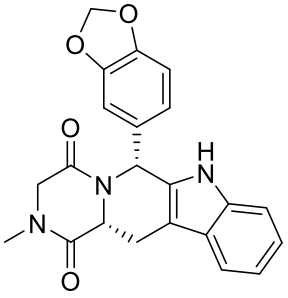


Figure 1. Visualization of the molecular docking validation result for the 1UDU receptor with an RMSD of 0.88 Å.

Molecular docking was conducted using Molegro Virtual Docker 5 with the receptor Phosphodiesterase-5A (PDB ID: 1UDU), which plays a crucial role in the pathophysiology of Erectile Dysfunction. Phosphodiesterase-5A (PDE5A) was identified as the key target protein associated with erectile dysfunction through network pharmacology analysis and pathway enrichment. In addition, PDE5A is the established molecular target of clinically used drugs such as sildenafil (Andersson, 2018). Receptor validation was performed through a redocking procedure using the native ligand Tadalafil. The redocking process produced an RMSD value of 0.88 Å, which is below the acceptable validation threshold of 2.0 Å. This result confirms that the docking protocol is reliable and capable of accurately reproducing the experimental binding orientation of the native ligand within the active site of the receptor(Putra *et al.*, 2016).

Table 1. Result Of Molecular Docking With Receptor PDE5 (PDB ID: 1UDU)

Coumpund	Rerank Score	Hbond	Steric Interaction
 41 (5-({4-[Butyl(hexyl)amino]-6-(pentylamino)-1,3,5-triazin-2-yl}amino)-2-methyl-1H-isoindole-1,3(2H)-dione)	-140,274	-	Met 816 Asn 662 Phe 820
 43 (5,7-Dimethoxy-3',4'-diprenyloxyisoflavone)	-138,157	Asn 662 (3,13 A)	Phe 786
	-137,391	-	Met 816 Phe 820 Gln 817

Obat Pembanding (vardenafil)			
	-134,826	Gln 817 (3,35 A)	Gln 817
Native Ligand (tadalafil)			

Docking analysis of phytochemical compounds from the 70% ethanol extract of *Uvaria rufa* roots revealed variations in binding affinity based on the rerank score values. Among the tested compounds, Compound 41 exhibited the lowest rerank score (–140.274 kcal/mol), followed by Compound 43 (–138.157 kcal/mol). Therefore, further validation through *in vitro* PDE5 enzyme inhibition assays and *in vivo* aphrodisiac activity studies is required to support the predicted biological activity of these compounds. *In vitro* assays are important to verify the inhibitory effect on PDE5, while *in vivo* studies may provide additional evidence regarding efficacy, pharmacological response, and safety in biological systems. Similar follow-up approaches have commonly been recommended in previous studies involving molecular docking and natural product-based drug discovery (Akdogan *et al*., 2024; Agu *et al*., 2023). These values indicate stronger predicted binding affinity compared with the reference drugs Vardenafil (–137.391 kcal/mol) and Tadalafil (–134.826 kcal/mol). In molecular docking analysis, a more negative rerank score generally reflects a stronger interaction between the ligand and the receptor active site, suggesting better binding stability and compatibility with the PDE5A catalytic pocket (Prasetiyo *et al.*, 2025).

Interaction analysis showed that Compound 41 formed steric interactions with amino acid residues Met816, Asn662, and Phe820. Notably, two of these residues (Met816 and Phe820) were also involved in the interaction profile of Vardenafil, indicating a similar binding orientation within the receptor binding pocket. Meanwhile, Compound 43 formed one hydrogen bond with Asn662 at a distance of 3.13 Å and one steric interaction with Phe786. Hydrogen bonds within the range of 2.6–3.5 Å are considered strong interactions that contribute significantly to ligand–receptor complex stability. Compound 41, a triazine derivative, demonstrated the most favorable interaction profile among the tested compounds. Triazine derivatives are not commonly reported as major secondary metabolites in the Annonaceae family, which is predominantly known to contain alkaloids, acetogenins, flavonoids, and terpenoids (Leboeuf et al., 1982). Isoflavone derivatives such as Compound 43 are more closely associated with naturally occurring phenolic metabolites found in medicinal plants and have been widely reported to exhibit various pharmacological activities, including antioxidant and vasodilatory effects (Dewick, 2009). Therefore, the occurrence of Compound 41 may represent a less commonly reported metabolite or a derivative identified during compound database screening. Further phytochemical investigations, including compound isolation and structural characterization, are required to confirm the natural origin and biosynthetic pathway of this compound in *Uvaria rufa*.

Overall, Compound 41 exhibited the most favorable interaction pattern and the strongest predicted binding affinity toward PDE5A, indicating its potential as a natural PDE5 inhibitor candidate for further investigation. In this study, PDE5A was selected as the primary therapeutic target because it plays a direct role in the cGMP signaling pathway responsible for corpus cavernosum vasodilation, which is the principal mechanism underlying penile erection.
Based on the pathway enrichment analysis, the cGMP signaling pathway demonstrated the highest relevance, with a count in network value of 2 out of 163 and the lowest false discovery rate (FDR). In contrast, PDE2A is more closely associated with cardiovascular regulation than erectile function. Previous studies have shown that increased PDE2A expression may protect against myocardial dysfunction, ventricular hypertrophy, fibrosis, and arrhythmias, highlighting its therapeutic potential as an antiarrhythmic and cardioprotective target (Samidurai et al., 2023). Therefore, PDE2A was considered less relevant for erectile dysfunction therapy because it does not directly contribute to the cGMP-mediated vasodilatory mechanism in the corpus cavernosum, unlike PDE5A. Consequently, PDE5A (PDB ID: 1UDU), with tadalafil as the native ligand and a well-established first-line therapy for erectile dysfunction, was selected as the receptor target in this study (Panjikar and Weiss, 2025).

Table 2. Result Of Physicochemical Prediction based on Lipinski's Rule of Five

Coumpound	Molecular Weight	Log P o/w	Hydrigen Bond		TPSA	Lipinski
	(<500 Da)	(<5)	Donor (<5)	Acceptor (<10)	(<140 Å²)	RO5
41 (5-({4-[Butyl(hexyl)amino]-6-(pentylamino)-1,3,5-triazin-2-yl}amino)-2-methyl-1H-isoindole-1,3(2H)-dione)	493,64	3,91	2	5	103,35 Å²	Yes
43 (5,7-Dimethoxy-3',4'-diprenyloxyisoflavone)	450,52	2,50	0	6	67,13 Å²	Yes
Obat Pembanding (vardenafil)	488,60	1,82	1	8	121,28 Å²	Yes
Native ligand (tadalafil)	387,38	1,45	1	4	74,87 Å²	Yes

Evaluation of physicochemical properties based on Lipinski's Rule of Five indicates that Compounds 41 and 43 satisfy all criteria, including molecular weight below 500 Da, log P below 5, hydrogen bond donors fewer than 5, hydrogen bond acceptors fewer than 10, and topological polar surface area (TPSA) below 140 $Å^2$. These parameters suggest good potential for passive diffusion through lipid membranes and favorable oral absorption, consistent with compounds that fulfill Lipinski's Rule of Five criteria (Muflihunna and Sukmawati, 2023). Based on the absorption prediction results, Compound 41 was classified as BCS class III due to its high solubility and low permeability, whereas Compound 43 was categorized as BCS class I because it exhibited high solubility and high permeability, indicating favorable gastrointestinal absorption. Pharmacokinetic analysis further showed that Compounds 41 and 43 had relatively high volume of distribution (Vd) values, suggesting extensive tissue distribution, while negative log BB values (<0.3) indicated low penetration through the blood–brain barrier and minimal central nervous system effects (Putra et al., 2025).

Table 3. Result OF Pharmacokinetic Prediction

Coumpound	Absorbtion		Distribution			Metabolism(CYP Inhibitor)					Excretion			Toxicity	
	Caco-2 Perm. (10^{-6} cm/s)	Log S	P-gp I Inh.	Vd (L/kg)	Log BB	2D6	3A4	1A2	2C19	2C9	Total Cl (L/hour/kg)	k (1/hour)	t½ (hour)	ORAT mol/kg (LD50)	Hepatotoksisitas
Native ligand	11,246	-3,50	No	0,972	-0,482	No	No	No	No	No	0,129	0,132	5,25	2,333	Yes
Vardenafil	8,953	-4,22	Yes	3,908	-1,466	No	Yes	No	No	Yes	0,147	0,037	18,729	2,032	Yes
5-({4-[Butyl(hexyl)amino]-6-(pentylamino)-1,3,5-triazin-2-yl}amino)-2-methyl-1H-isoindole-1,3(2H)-dione)	2,2029	-6,50	No	3,280	-1,527	No	Yes	No	Yes	Yes	0,231	0,070	9,9	2,365	Yes
43(5,7-Dimethoxy-3',4'-diprenyloxyisoflavone)	14,859	-6,22	No	2,213	-0,404	No	Yes	No	Yes	Yes	0,219	0,098	7,071	2,793	No

Both compounds were also predicted to inhibit CYP3A4, CYP2C9, and CYP2C19 enzymes, suggesting potential drug–drug interactions. In terms of elimination, Compounds 41 and 43 were categorized as intermediate half-life compounds, indicating moderate duration of action and potentially feasible dosing regimens. Compared with established PDE5 inhibitors, tadalafil has a longer half-life of approximately 17.5 hours, whereas vardenafil exhibits a shorter half-life of approximately 4–5 hours (Keating and Scott, 2003; Heck et al., 2002). These findings suggest that Compounds 41 and 43 may possess pharmacokinetic properties supportive of further development as PDE5 inhibitor candidates. Based on toxicity prediction, all compounds except Compound 43 were predicted to be non-hepatotoxic, while Compound 43 showed the lowest LD_{50} value, indicating relatively higher acute toxicity (Putra et al., 2025). The TPSA values of Compound 41 (103.35 $Å^2$) and Compound 43 (67.13 $Å^2$) fall within the optimal range that supports efficient gastrointestinal absorption while maintaining sufficient polarity for biological interactions. Reference drugs such as vardenafil and tadalafil also display TPSA values consistent with orally active therapeutic agents. Overall, the Lipinski parameters and TPSA evaluation demonstrate that both compounds possess physicochemical characteristics suitable for development as oral drug candidates(Shofa *et al.*, 2022

Pharmacokinetic prediction using the ADMET approach further supports the potential of these compounds. In the absorption phase, Compound 41 is classified as Biopharmaceutics Classification System Class III, while Compound 43 belongs to Biopharmaceutics Classification System Class I, indicating favorable gastrointestinal absorption potential. Both compounds show high predicted volumes of distribution, suggesting wide distribution into body tissues, while negative log BB values indicate limited penetration across the blood–brain barrier and a low likelihood of central nervous system effects. In the metabolism phase, both compounds are predicted to inhibit several cytochrome P450 enzymes, including CYP3A4, CYP2C9, and CYP2C19, which may increase the risk of drug–drug interactions.

The predicted metabolic profile of Compounds 41 and 43 indicates potential clinical implications regarding their safety as therapeutic candidates. Both compounds were predicted to inhibit CYP3A4, CYP2C9, and CYP2C19 enzymes, suggesting the possibility of drug–drug interactions due to altered drug metabolism. CYP3A4 inhibition is particularly important because this enzyme is involved in the metabolism of many clinically used drugs, including PDE5 inhibitors. Increased plasma drug concentrations caused by CYP inhibition may enhance pharmacological effects but may also increase the risk of adverse effects and toxicity. Therefore, understanding the metabolic characteristics of these compounds is essential for evaluating their safety, interaction potential, and suitability for long-term therapeutic use (Djebli et al., 2022; Yu et al., 2021). Excretion analysis suggests moderate elimination rates with predicted ultra-intermediate half-lives, indicating the potential for once- or twice-daily dosing. Toxicity prediction shows that most compounds, including tadalafil and vardenafil, exhibit potential hepatotoxicity, while Compound 43 demonstrates a relatively safer toxicity profile. Collectively, these results suggest that Compounds 41 and 43 possess promising binding affinity, favorable physicochemical properties, and acceptable pharmacokinetic profiles for further investigation as potential natural PDE5 inhibitors (Putra *et al.*, 2025).

Conclusion

Both of 5-({4-[butyl(hexyl)amino]-6-(pentylamino)-1,3,5-triazin-2-yl}amino)-2-methyl-1H-isoindole-1,3(2H)-dione and 5,7-dimethoxy-3',4'-diprenyloxyisoflavone demonstrated strong binding affinity toward PDE5A in molecular docking simulations. Nevertheless, 5,7-dimethoxy-3',4'-diprenyloxyisoflavone displayed a more favorable pharmacokinetic and toxicity profile based on ADMET prediction. Indicating its potential as the most promising candidate for further development as an anti-erectile dysfunction agent.

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References

Aghahosseini, F., Bayat, M., Sadeghian, Z., Gheidari, D., & Safari, F. (2024). Synthesis, molecular docking study, MD simulation, ADMET, and drug likeness of new thiazolo [3, 2-a] pyridine-6, 8-dicarbonitrile derivatives as potential anti-diabetic agents. *PLoS One, 19*(9), e0306973.

Agu, P. C., Afiukwa, C. A., Orji, O. U., Ezeh, E. M., Ofoke, I. H., Ogbu, C. O., Ugwuja, E. I., & Aja, P. M. (2023). Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. *Scientific reports, 13*(1), 13398. https://doi.org/10.1038/s41598-023-40160-2

Akdogan, N., Rawat, R., Ozden, T., Uzan, F., Deger, M., YILMAZ, I., ... & ARIDOGAN, I. (2024). Molecular docking and dynamics simulation analysis of PDE5 inhibitor candidates for erectile dysfunction treatment. *European Review for Medical & Pharmacological Sciences, 28*(20).

Amrulloh, L. S. W. F., Harmastuti, N., Prasetiyo, A., & Herowati, R. (2023). Analysis of molecular docking and dynamics simulation of mahogany (Swietenia macrophylla King) compounds against the PLpro enzyme SARS-COV-2. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, *10*(3), 347-359.

Andersson, K.-E. (2018) PDE5 inhibitors – pharmacology and clinical applications 20 years after sildenafil discovery. *British Journal of Pharmacology, 175*: 2554–2565. doi: 10.1111/bph.14205.

Dahril (2017) 'Disfungsi Ereksi', National symposium & workshop "Aceh Surgery Update 2", 1(September), pp. 63–79.

Dewick, P.M. (2009). *Medicinal Natural Products: A Biosynthetic Approach. 3rd* edn. Chichester: Wiley.

Djebli, N., Fabre, I., Boulenc, X. and Nicolas, O. (2022) 'Cytochrome P450 inhibition and drug–drug interaction potential in drug development', *Pharmaceuticals*, 15(7), 844. https://doi.org/10.3390/ph15070844

Hidayah, N., Permatasari, L., Rosmalina Hidayati, A., & Muliasari, H. (2024). In Silico Analgesic and Toxicity Analysis of Modified Paracetamol on COX-2 Receptor (PDB ID: 3LN1). *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia, 11* (3).

Imran, M., Jawaid, T., Alhuthali, H.M., Alrehaili, A.A., Alzahrani, A.R., Rehman, Z.U., Mbunge, E., Dzinamarira, T., 2025, Quantum-mechanically refined, dynamics-coupled, and AI-augmented elucidation of epigenetic inhibition: an in silico paradigm targeting HDAC8 of *Schistosoma mansoni*, *Journal of Tropical Medicine* 2025, 1172449. https://doi.org/10.1155/jotm/1172449

Isyrafi, M.A. (2024) Metabolite profiling ekstrak etanol 70% radiks lelak (Uvaria rufa Blume) menggunakan metode UPLC-QToF-MS/MS. Skripsi. Malang: Program Studi Farmasi Fakultas Kedokteran dan Ilmu Kesehatan, Universitas Islam Negeri Maulana Malik Ibrahim.

Kurnia, K. A. *et al.* (2019) 'Understanding the effect of pH on the solubility of Gamavuton-0 in the aqueous solution: Experimental and COSMO-RS modelling', *Journal of Molecular Liquids*, 296, p. 111845. doi: 10.1016/J.MOLLIQ.2019.111845.

Leboeuf, M. et al. (1982). The phytochemistry of the Annonaceae. *Phytochemistry, 21*(12), pp. 2783–2813.

Muflihunna, A. and Sukmawati, S. (2023) 'In Silico Study Of Java Wood (Lannea Coromadelica) As Anti- Inflammatory In TNF-A And Cox-2 Mediators. *Indonesian Journal of Pharmaceutical Science and Technology.*

Panjikar, S. and Weiss, M.S. (2025) 'Peptide bonds revisited', *IUCrJ*, 12(Pt 3), pp. 307–321. Available at: https://doi.org/10.1107/S2052252525002106.

Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. *Journal of Medicinal Chemistry, 58*(1), 4066-4072.

Prasetiyo, A. *et al.* (2025) 'In silico discovery of potential sodium-glucose cotransporter-2 (SGLT-2) inhibitors from Smallanthus sonchifolius (Poepp.) H.Rob. via molecular docking and molecular dynamics simulation approach', *Journal of Pharmacy and Pharmacognosy Research*, 13(3), pp. 716–728. Available at: https://doi.org/10.56499/jppres24.2104_13.3.716.

Putra, G. S.; Sulistyowaty, M. I.; Yahmin, Y.; Sumari, S.; Retnosari, R.; Suhud, F.; Kesuma, D.; Mardianto, R.; Sukkaew, A. and Yamauchi, T., 2025, In silicoand in vitro antimalarial activity evaluation of eugenol transformation products against Plasmodium falciparum strain 3D7, *Journal of Tropical Pharmacology*, 13:1–10.

Putra, G.S. *et al.* (2016) 'Synthesis, molecular docking study and brine shrimp lethality test of benzoxazine and aminomethyl derivatives from eugenol', *International Journal of Pharma Research & Review*, 5(4), pp. 1–11. Putra, G.S. *et al.* (2025) 'In silico and in vitro

antimalarial activity evaluation of eugenol's transformation products against Plasmodium falciparum strain 3D7 using the Trager and Jensen method', *Journal of Pharmacy & Pharmacognosy Research*, 13(s1), pp. S347– S370. Available at: https://doi.org/10.56499/jppres24.2286_13.s1.347.

Shofa, A.F. *et al.* (2022) 'Studi Penambatan Maya dan Prediksi Toksisitas Turunan 5-Fluorouridin Monofosfat Pada Enzim Orotidin-5-monofosfat Dekarboksilase', 3(2), pp. 91–98. Available at: https://doi.org/10.15408/pbsj.v3i2.24524.

Siswandono (2016) *Kimia Medisinal Jilid Satu*. 2nd edition. Surabaya: Universitas Airlangga. Sulistyowaty, M. I.; Putra, G. S.; Budiati, T.; Indrianingsih, A. W.; Renawanti, Y. W.; Nofianti,K. A.; Ekowati, J.; Purwitasari, N.; Saechan, C.; Zidan, S. A. H. and Yamauchi, T, 2025, Synthesis and docking studies of the functionalized dibenzylideneacetones as promising antimalarial agents, *Journal of Pharmacy and Pharmacognosy Research*, 13(2): 416– 430.

Taek, M.M. et al. (2024) Aktivitas Afrodisiak In Vivo Ekstrak Etanol 70 % Akar Lelak (*Uvaria rufa Blume* .) Pada Mencit (Mus musculus), 12(2), pp. 1904–1912.

Taek, M. M., Ma'arif, B., Nurmawati, D., Maulina, N., Dahayu, D., Isyrafi, M. A., ... & Muslikh, F. A. (2025). Metabolite profiling of ethanol extract of radix Uvaria rufa blume by UPLC-QToF-MS/MS and its potential aphrodisiac activity. *Asian Journal of Green Chemistry*, *9*(4), 985-1003.

Tienforti, D., Felzani, G., Di Pasquale, A. B., & Barbonetti, A. (2025). Which PDE5 inhibitor is the most effective in the treatment of erectile dysfunction in men with spinal cord injury? A systematic review and network meta-analysis. *Andrology*, *13*(2), 314-322Kurnia, K. A. *et al.* (2019) 'Understanding the effect of pH on the solubility of Gamavuton-0 in the

aqueous solution: Experimental and COSMO-RS modelling', *Journal of Molecular Liquids*, 296, p. 111845. doi: 10.1016/J.MOLLIQ.2019.111845.

Tenggara, K.A. and Yassir, M. (2018) 'Jurnal Biotik', 6(1), pp. 17–34.