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Research Article

Study of Molecular Docking, Pharmacokinetics, and Toxicity Study of Active Compounds from Durian (*Durio zibethinus*) Peel as SAP4-6 And ERG11 Antagonists in *Candida albicans*

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Abstract
Candidiasis is a prevalent of fungal infection in tropical countries including Indonesia, with *Candida albicans* as the main causative agent (70–80%). *C. albicans* possesses key virulence factors including secreted aspartyl proteinase (SAP) and ERG11, which play crucial roles in pathogenesis and antifungal resistance. Durian peel (*Durio zibethinus*) is rich in bioactive compounds such as phenolics, flavonoids, and coumarins with potential antifungal properties, yet their mechanism of action remains poorly understood. This study aimed to investigate the potential of durian peel compounds as antagonists of SAP4-6 and ERG11 in *C. albicans*. This research employed an *in silico* bioinformatics approach. From 25 durian peel compounds analyzed, those meeting drug-likeness criteria were selected for molecular docking against target proteins SAP4-6 and ERG11, followed by pharmacokinetic and toxicity analyses. Eight compounds met drug-likeness criteria. Molecular docking results revealed several compounds with stronger binding affinities compared to the control (fluconazole), namely catechin (-7.1 kcal/mol) and epicatechin (-6.5 kcal/mol) for SAP4, cleomiscosin A (-9.1 kcal/mol) and cleomiscosin B (-9.2 kcal/mol) for SAP5, epicatechin and cleomiscosin A (-7.3 kcal/mol) for SAP6, and cleomiscosin A (-8.7 kcal/mol) and cleomiscosin B (-8.4 kcal/mol) for ERG11. Pharmacokinetic analysis showed these compounds possess good intestinal absorption and low toxicity profiles. Cleomiscosins A and B demonstrated the best potential as SAP4-6 and ERG11 antagonists in *C. albicans* with favorable pharmacokinetic and toxicity profiles.

Keywords: *Candida albicans*, durian peels, SAP4-6, ERG11, molecular docking

1. INTRODUCTION

Fungal infections are a significant cause of diseases, particularly in tropical countries such as Indonesia. Among the many types of fungi, the *Candida* species stand out for their prevalence and pathogenicity. Diseases caused by *Candida*, commonly referred to as candidiasis, range from acute to subacute forms and occur globally, affecting individuals of all age groups and genders. Among these species, *Candida albicans* is the most common, accounting for 70–80% of infections, followed by *Candida tropicalis*, which contributes 30–40% [1][2]. *C. albicans* is a normal flora found in various parts of the human body, including the vagina, skin, subungual regions, gastrointestinal tract, respiratory tract, and mucosal membranes. However, in individuals with compromised or suppressed immune systems, *C. albicans* can cause severe systemic diseases [3]. Globally, the prevalence of *C. albicans* varies, being the third most common cause of fungal infections in children in the United States and Europe, with prevalence rates ranging from 37% in Latin America to 70% in Norway. Epidemiological studies in Asia also indicate a high prevalence, with *C. albicans* accounting for 56.0% of cases in Hong Kong, 33.3% in Singapore, 55.5% in Taiwan, and 41.0% in Japan [4]. In Indonesia, candidiasis prevalence reaches 20–25%, making it the third most common dermatophytosis in the country [5][6].

Several virulence and adaptation factors contribute to the pathogenicity of *C. albicans*, including adhesion/invasion capabilities, phenotype switching, proteinase production, nutrient acquisition, environmental adaptation, and drug resistance. Among these, proteinase enzymes are considered a primary virulence factor critical to *C. albicans* pathogenicity [7]-[9]. These enzymes break down peptide bonds in proteins through hydrolysis, enabling the fungus to acquire nutrients, invade host tissues, and evade immune responses. The most significant hydrolytic enzyme secreted by *C. albicans* is secreted aspartyl proteinase (SAP), alongside phospholipase and lipase, with SAP

Figure 1. Drug-likeness analysis.

Compounds	WLOG P	XLOG P	MLOG P	H_Acceptors	H_Donors	Molar Refractivity	Molecular Weight	TPSA	#Rotatable Bonds	Lipinski	Ghose	Veber	Egan	Muegge
Cleomiscosin B	2.06	2.12	0.66	8	2	98.82	386.35	107.59	4	0	0	0	0	0
Quercetin	1.99	1.54	-0.56	7	5	78.04	302.24	131.36	1	0	0	0	0	0
Catechin	1.22	0.36	0.24	6	5	74.33	290.27	110.38	1	0	0	0	0	0
Epicatechin	1.22	0.36	0.24	6	5	74.33	290.27	110.38	1	0	0	0	0	0
Cleomiscosin A	2.06	2.12	0.66	8	2	98.82	386.35	107.59	4	0	0	0	0	0
Fraxidin	1.52	1.50	0.49	5	1	57.49	222.19	68.90	2	0	0	0	0	0
Sinapic Acid	1.40	1.46	0.73	5	2	58.12	224.21	75.99	4	0	0	0	0	0
Fraxetin	1.21	1.17	0.20	5	2	53.02	208.17	79.90	1	0	0	0	0	0
Flucona zole*	1.47	0.35	1.47	7	1	70.71	306.27	81.65	5	0	0	0	0	0

*Control

being the most dominant. Classified as SAP1–10, these enzymes perform various roles in virulence. They digest molecules for nutrition, disrupt host cell membranes for tissue invasion, and evade antimicrobial responses. Studies on animals infected with mutant *C. albicans* strains lacking SAP4-6 genes have demonstrated prolonged survival compared to those infected with wild-type strains, underscoring the critical role of SAP4-6 in the fungus's virulence, pathogenesis, and morphogenesis [10][11].

In addition to proteinases, the ERG11 enzyme, which encodes lanosterol 14-α-demethylase, plays a crucial role in sterol biosynthesis. ERG11 is also involved in antifungal resistance, particularly against azole drugs. Mechanisms of resistance related to ERG11 include point mutations, genomic plasticity, and overexpression of the gene, which alter drug accessibility to the enzyme's active site. This enzyme also influences membrane permeability, fluidity, enzyme activity, cell shape, and cell cycle progression in *C. albicans* [12][13]. The increasing resistance of *C. albicans* to antifungal agents highlights the need for natural inhibitors targeting SAP4-6 and ERG11. Plant-derived phytochemicals can inhibit active sites of virulence enzymes like SAP. These natural compounds act as potential inhibitors by competing with substrates, neutralizing enzyme effects, and reducing the severity of virulence [14].

Durian rind (*Durio zibethinus*), a natural resource abundant in Indonesia, contains bioactive compounds such as phenolics, flavonoids, saponins, tannins, and coumarins [15]. These compounds possess pharmacological properties and have shown antifungal activity against *C. albicans* [16][17]. For instance, ethanol extracts of durian rind effectively inhibit fungal growth at a concentration of 6.25%, with a minimum inhibitory concentration (MIC) of 0.78% and a minimum bactericidal concentration (MBC) of 3.125% [18]. Specific compounds like quercetin and coumarin have been tested through in silico methods, demonstrating the ability to inhibit enzyme active sites and reduce virulence levels with binding energies of -5.57 and -5.84 kcal/mol for quercetin and coumarin, respectively [19]. To enhance the antifungal potential of durian rind bioactive compounds, computational and information technologies offer promising avenues

for drug discovery. *In silico* bioinformatics, a branch of computational science, involves the use of molecular structure databases for targeted protein analysis [20]. This approach is widely adopted in drug development, as it facilitates the prediction of pharmacokinetic profiles and toxicity of potential drug candidates using tools such as pkCSM and ADMET predictor. The study aims to investigate the molecular docking of durian rind active compounds against SAP4-6 and ERG11 proteins in *C. albicans* and analyze their pharmacokinetics and toxicity profiles. The goal is to identify potential antifungal agents from durian rind, contributing to the development of safer and more effective treatments for *C. albicans* infections.

2. MATERIALS AND METHODS

The research design utilized in this study is exploratory and employs an *in silico* approach to investigate the effects of bioactive compounds from durian rind (*D. zibethinus*) on the SAP4-6 and ERG11 target proteins of *C. albicans*. This is achieved through molecular docking studies and the analysis of pharmacokinetics and toxicity profiles. The bioactive compounds were selected from phenolic acids, phenolic glycosides, flavonoids, and coumarins listed in the PubChem database. The compounds were prepared in their structural file format (.sdf) for molecular docking, allowing for detailed interaction analysis with the target proteins.

The research variables include independent variables, represented by the bioactive compounds from durian rind, and dependent variables, such as binding affinity, molecular properties (e.g., molecular weight (MW), lipophilicity (log P), hydrogen bond donors and acceptors, and topological polar surface area (TPSA)), and pharmacokinetic and toxicological profiles. Computational tools such as AutoDock Vina, BIOVIA Discovery Studio, OpenMM, PkCSM, and SwissADME were utilized to process, analyze, and visualize the data. The research was conducted using computational resources and web-based tools, with the protein structures for SAP4-6 and ERG11 sourced from the RCSB PDB and UniProt databases, and bioactive compound data obtained from PubChem. The study aims to identify promising compounds with high binding affinity and favorable pharmacokinetic and toxicological profiles to serve as potential antifungal agents against *C. albicans*.

3. RESULTS AND DISCUSSION

3.1. Drug-likeness of Durian Rind Compounds

The drug-likeness test is an initial stage in drug development to ensure that a molecule meets the ideal pharmacokinetic characteristics. SwissADME, a tool developed by Daina et al. [21], provides a comprehensive analysis of the physicochemical and pharmacokinetic properties of molecules, including evaluations based on various rules such as Lipinski's rule of five, Veber's rule, Ghose filter, Egan's rule,

Table 2. Binding affinity of target proteins with durian rind compounds and control.

Ligand	Binding Affinity (kcal/mol)			
	SAP 4	SAP 5	SAP 6	ERG11
Quercetin	-6.4	-8.5	-7.2	-8.3
Catechin	-7.1	-8.0	-6.8	-8.2
Epicatechin	-6.5	-7.4	-7.3	-7.9
Cleomiscosin_A	-5.9	-9.1	-7.3	-8.7
Cleomiscosin_B	-6.3	-9.2	-6.2	-8.4
Fraxetin	-6.0	-6.9	-6.3	-7.1
Fraxidin	-6.0	-6.5	-6.4	-6.7
Sinapic Acid	-6.4	-6.2	-5.9	-5.8
Fluconazole*	-6.4	-7.3	-7.0	-7.1

*Control

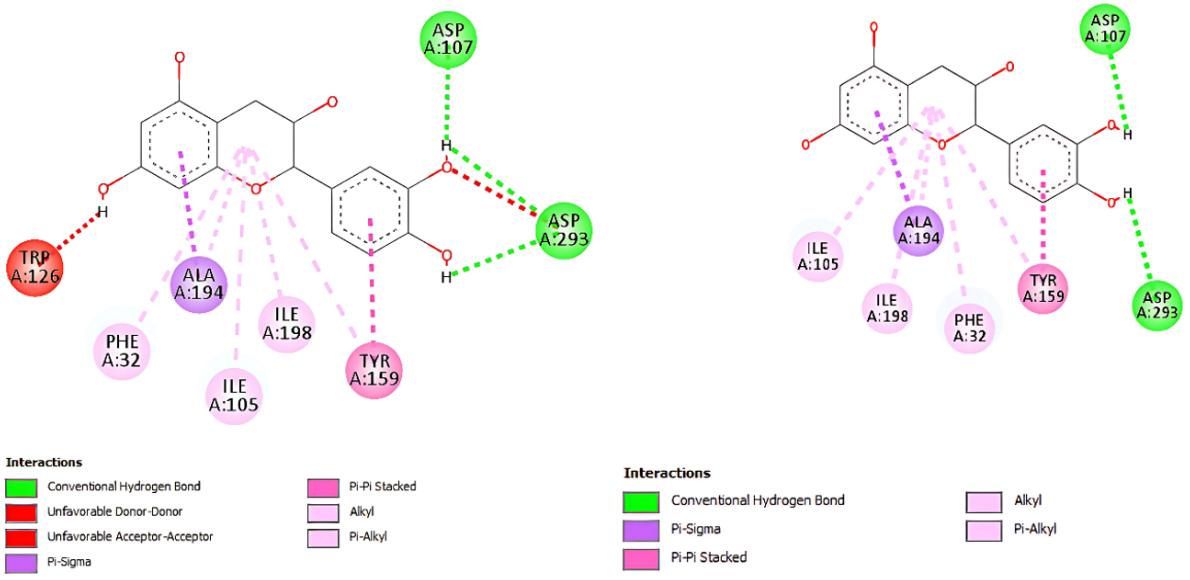
Table 3. Interaction of Amino Acid Residues and Shortest Distance of Compounds with the Best Binding Affinities for Each Receptor.

Docking Complex	Hydrogen Bond	Other Interaction	Shortest Interaction Distance (Å)
SAP4–Catechin	**Asp107**, **Asp293**	Phe32, **Ile105**, Trp126, **Tyr159**, **Ala194**, **Ile198**	1.43
SAP4-Epicatechin	**Asp107**, **Asp293**	Phe32, **Ile105**, **Tyr159**, **Ala194**, **Ile 198**	2.37
SAP5-Cleomiscosin A	-	Ile30, **Tyr84**, **Asp86**, **Tyr225**	3.66
SAP5-Cleomiscosin B	**Gly220**	**Ile12**, Ile30, **Tyr84**, **Gly85, Ala119**, **Arg120**, **Leu216, Tyr225**, **Ile305**	2.55
SAP6-Cleomiscosin A	**Lys159**	**Asp108, Tyr160**, **Ala161**, Asp162, **Tyr301**	3.73
SAP6-Epicatechin	**Ala161**, Asp162	**Asp294**	2.33
ERG11-Cleomiscosin A	Ile304, Thr311	**Ile131**, Leu200, Leu204, Phe475	2.81
ERG11-Cleomiscosin B	-	**Phe126**, **Il e 131**, **Tyr132**, **Phe228, Il e 379**	4.78

and Muegge's rule. This analysis examines parameters such as MW, log P, hydrogen bond donors and acceptors, TPSA, and the number of rotatable bonds—all contributing to ADME predictions. This study utilized 25 bioactive compounds derived from durian rind, categorized into phenolic acids and glycosides (benzoic acid, glucopyranosyl-4-methoxy-cinnamic acid, 3,4-dihydroxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid, ethyl protocatechuate, 3,4-dihydroxybenzaldehyde, caffeic acid, sinapic acid, vanillic acid, and leonuriside A), flavonoids (quercetin, quercitrin, rutin, quercetin 3-O-rhamnoside, quercetin 3-O-glucoside, catechin, epicatechin, procyanidin B, and malvidin-3-O-glucoside), and coumarins (coumarin, scopoletin, fraxetin, fraxidin, cleomiscosin A, and cleomiscosin B). These compounds were evaluated for their drug-likeness properties as part of the initial stages of the research to determine their potential as anti-Candida drug candidates.

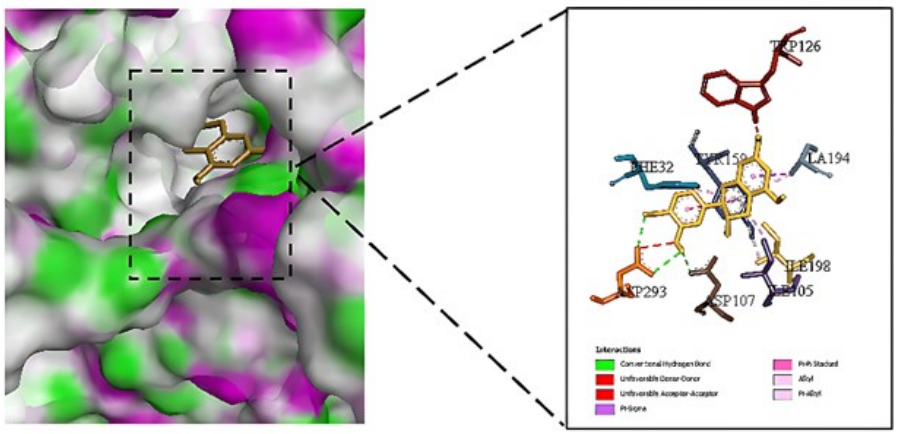
The drug-likeness analysis involved applying Lipinski's Rule of Five, where eligible compounds must have a molecular weight of less than 500 Da, log P below 5, hydrogen bond donors (HBD) under 5, and hydrogen bond acceptors (HBA) under 10. Additional criteria included Ghose's rule (20–70 atoms, molecular weight 160–480, refractivity 40–130, WLogP -0.4 to 5.6), Veber's rule (fewer than 10 rotatable bonds, TPSA below 140), Egan's rule (WLogP under 5.88, TPSA under 131.6), and Muegge's rule (MW 200–600 Da, fewer than 7 aromatic rings, fewer than 1 heteroatom, fewer than 10 HBA, fewer than 5 HBD, XLog P -2 to 5, fewer than 15 rotatable bonds, and TPSA below 150) [15]-[19]. Among the compounds analyzed, eight compounds from durian rind fulfilled all these criteria, making them strong candidates for further study as anti-Candida agents.

As shown in Table 1, the durian rind compounds that meet the criteria of Lipinski, Ghose, Veber, Egan, and Muegge rules are cleomiscosin B, quercetin, catechin, epicatechin, cleomiscosin A, fraxidin, sinapic acid, and fraxetin. Table 1 indicates that fraxetin has the lowest MW (208.17), while cleomiscosins A and B have the highest MW (386.35), suggesting that fraxetin is more water-soluble. The lowest WLog P value is found in fraxetin (1.21), while the highest is in cleomiscosin A and B (2.06). The lowest XLogP value is recorded for catechin and epicatechin (0.36), with the highest in cleomiscosins A and B (2.12). Regarding MLogP, the lowest value is in quercetin (-0.56), and the highest is in sinapic acid (0.73).



(**A**) (**B**)

Figure 1. 2D visualization of protein-ligand interactions: (A) SAP4-catechin and (B) SAP4-epicatechin.



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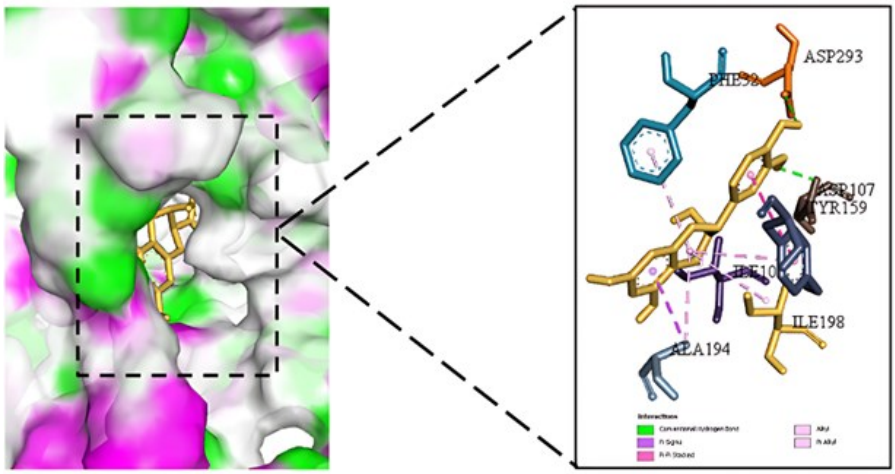
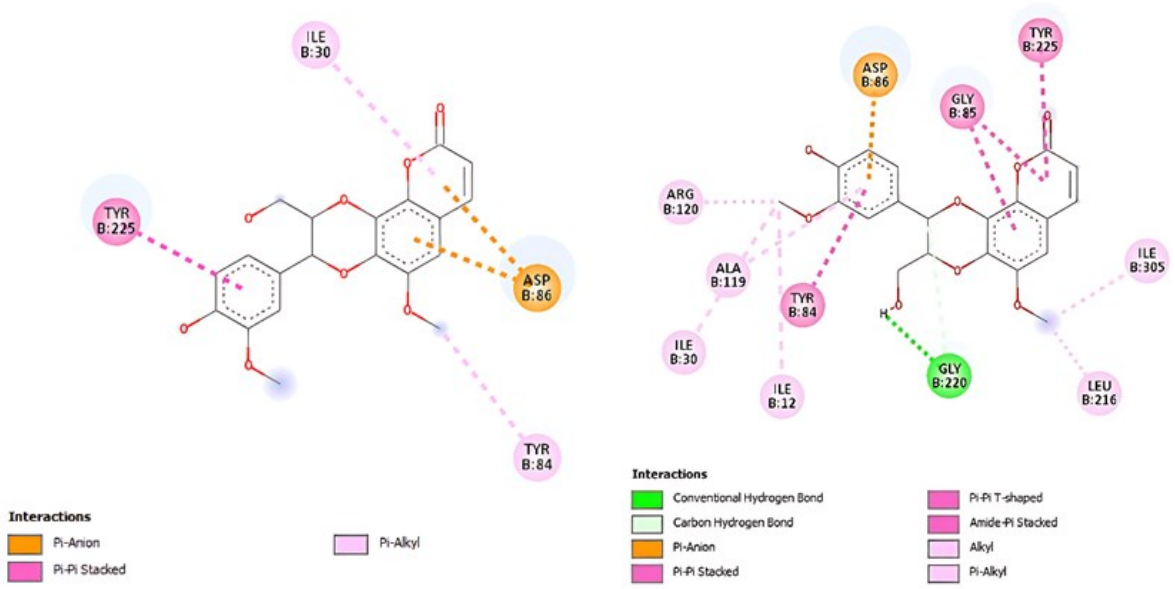


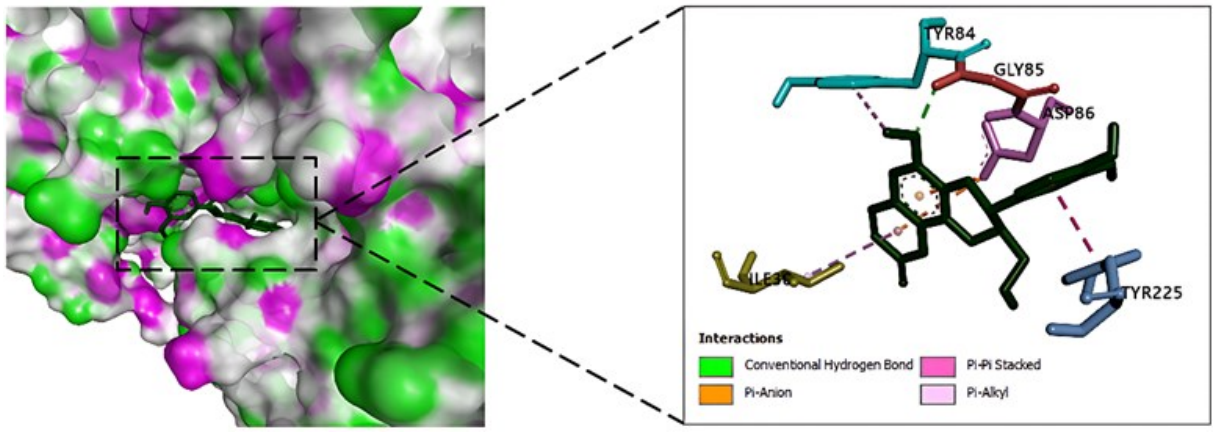
(**B**)

Figure 2. 3D visualization of protein-ligand interactions: (A) SAP4-catechin and (B) SAP4-epicatechin.



(**A**) (**B**)

Figure 3. 2D visualization of protein-ligand interactions: (A) SAP5-cleomiscosin A and (B) SAP5-cleomiscosin B.



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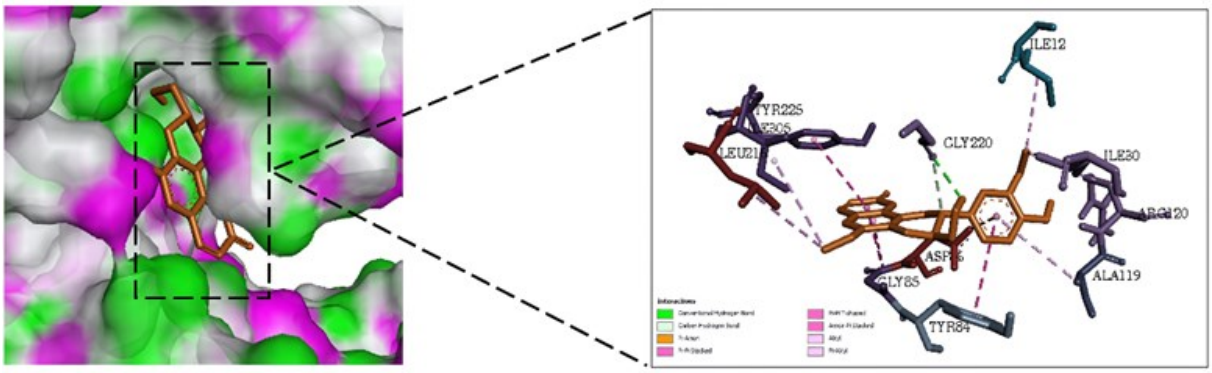


(**B**)

Figure 4. 3D visualization of protein-ligand interactions: (A) SAP5-cleomiscosin A and (B) SAP5-cleomiscosin B.

These values indicate that fraxetin, catechin, epicatechin, and quercetin exhibit hydrophilic properties. The HBD count ranges from 1 to 5, while the HBA count is between 5 and 8, demonstrating that all eight compounds possess lipophilic characteristics. Additionally, the molar refractivity values are highest for cleomiscosins A and B (98.82) and lowest for fraxetin (53.02), indicating that these molecules have adequate size and polarizability for interaction with biological receptors. Lastly, the TPSA values of all compounds are ≤ 140 Å², which suggests good oral bioavailability [20].

3.2. Molecular Docking of Durian Rind Compounds on C. albicans Proteins

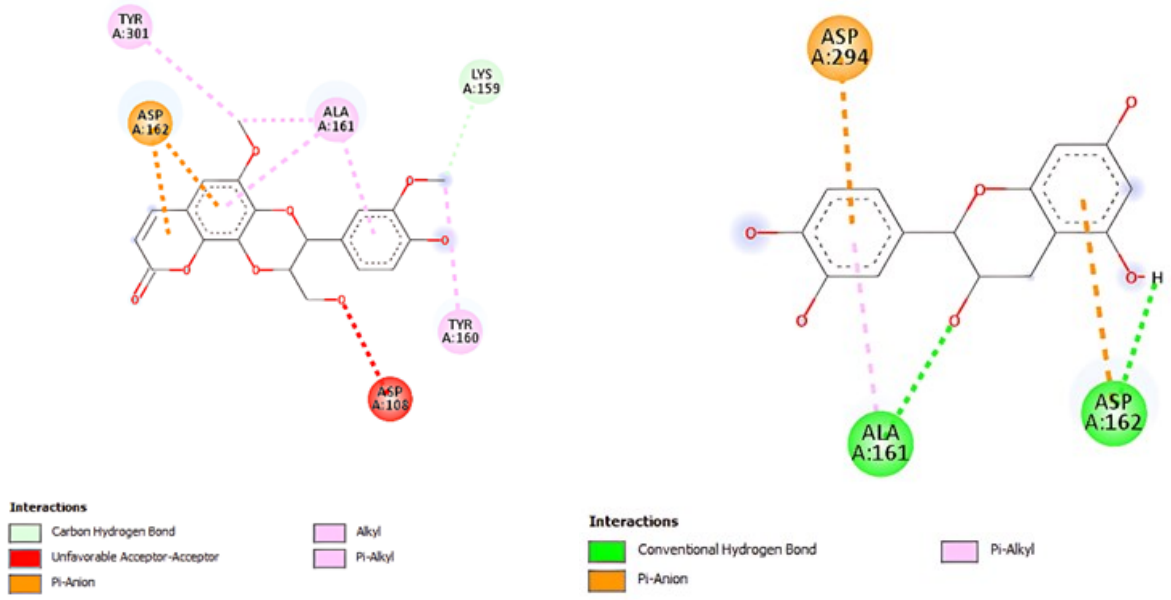
Based on the drug-likeness analysis, the eight compounds with favorable profiles were selected for the next stage of the study. The subsequent analysis involved molecular docking to evaluate the binding of durian rind compounds to the SAP4-6 and ERG11 proteins of *C. albicans*. As shown in Table 2, several durian rind compounds exhibited lower binding affinities compared to the control (fluconazole), indicating potentially stronger and more stable interactions with the target proteins. These compounds included catechin and epicatechin for SAP4, with binding affinity values of -7.1 and -6.5 kcal/mol, respectively; cleomiscosins A and B for SAP5, with values of -9.1 and -9.2 kcal/mol; epicatechin and cleomiscosin A for SAP6, both at -7.3 kcal/mol; and cleomiscosins A and B for ERG11, with values of -8.7 and -8.4 kcal/mol, respectively.

Fluconazole, a commonly prescribed antifungal drug, was used as the control in this study. Compounds with lower binding affinity values compared to the control are predicted to have stronger and more stable binding to the target proteins than fluconazole [22]. On the other hand, compounds such as cleomiscosin A for SAP4 and sinapic acid for SAP5, SAP6, and ERG11 exhibited higher binding affinity values than the control, indicating weaker interactions with the target proteins. This suggests that compounds with lower binding affinity values, such as catechin, epicatechin, and cleomiscosin derivatives, may have greater potential as antifungal agents against *C. albicans* [23].

The amino acid residues involved in protein-ligand interactions exhibit variation, as shown in Table 3. The visualizations can also be presented in both 2D and 3D graphical formats. For SAP4, the interaction with catechin involves amino acid residues Phe32, Ile105, Asp107, Trp126, Tyr159 Ala194, Ile198, and Asp293 (Figures 1 (A) and 2 (A)). The residues involved in the interaction between SAP4 and epicatechin include Phe32, Ile105, Asp107, Tyr159, Ala194, Ile198, and Asp293 (Figures 1 (B) and 2 (B)). The residues Phe32, Ile105, Asp107, Tyr159, Ala194, Ile198, and Asp293 are common in both SAP4-catechin and SAP4-epicatechin interactions, indicating their critical role in the binding of these ligands. These residues could be key targets for structural modifications of the ligands to enhance their effectiveness and selectivity toward SAP4. These interactions occur at the active site of SAP4, consistent with findings from a study conducted by Meylani et al. [24].

For SAP5, the interaction with cleomiscosin A involves the amino acid residues Ile30, Asp86, Tyr84, and Tyr225 (Figures 3 (A) and 4 (A)). The residues involved in the interaction of SAP5 with cleomiscosin B include Ile12, Ile30, Tyr84, Gly85, Ala119, Arg120, Leu216, Gly220, Tyr225, and Ile305 (Figures 3 (B) and 4 (B)). The residues Ile30, Tyr84, and Tyr225 are common to both interactions, indicating their critical role in binding these ligands. These residues could serve as focal points for ligand structural modifications to enhance effectiveness and selectivity against SAP5. These interactions occur at the active site of SAP5, consistent with the findings of Meylani et al. [24].

For SAP6, the interaction with cleomiscosin A involves the amino acid residues Asp108, Lys159, Tyr160, Ala161, Asp162, and Tyr301 (Figures 5 (A) and 6 (A)). The residues involved in the interaction of SAP6 with Epicatechin are Ala161, Asp162, and Asp294 (Figures 5 (B) and 6 (B)). The residues Ala161 and Asp162 are common to both interactions, indicating their significant role in ligand binding. These residues could be targeted for ligand modification to improve efficacy and selectivity against SAP6. These interactions also occur at the active site of SAP6, consistent with the research of Meylani et al. [24].



(**A**) (**B**)

Figure 5. 2D visualization of protein-ligand interactions: (A) SAP6-cleomiscosin A and (B) SAP6-epicatechin.

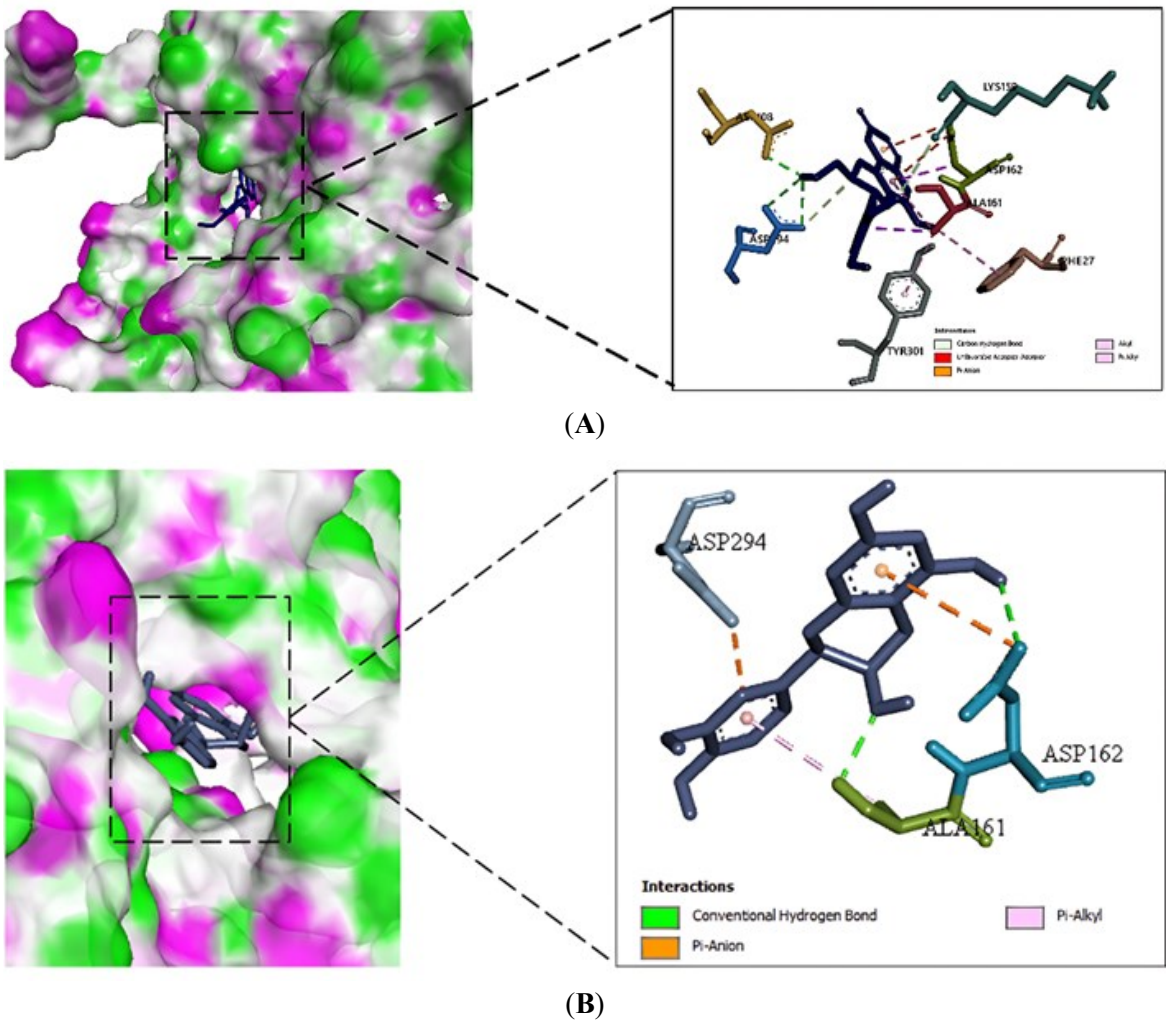


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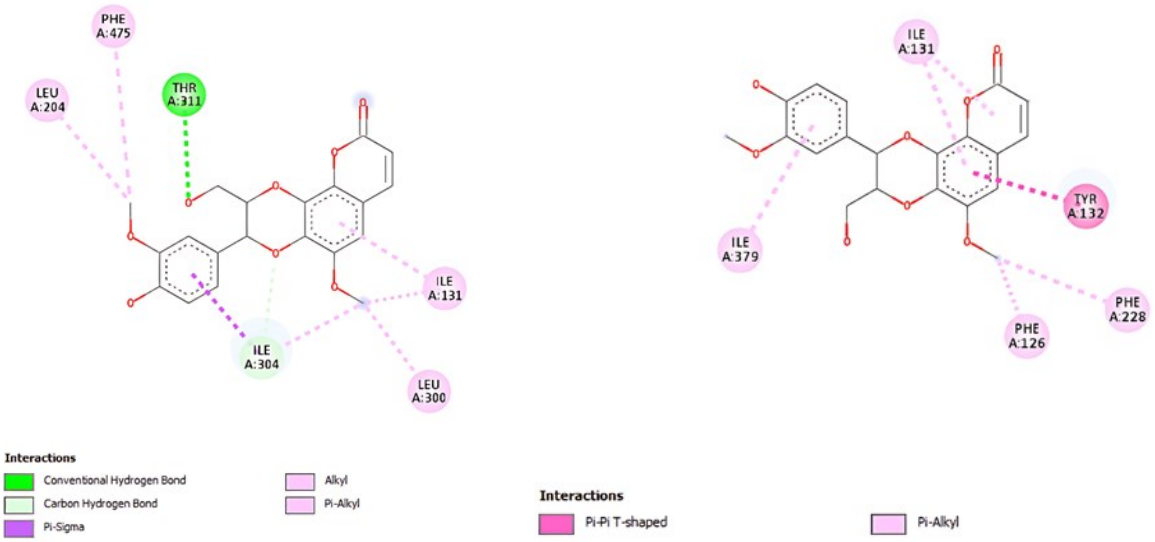
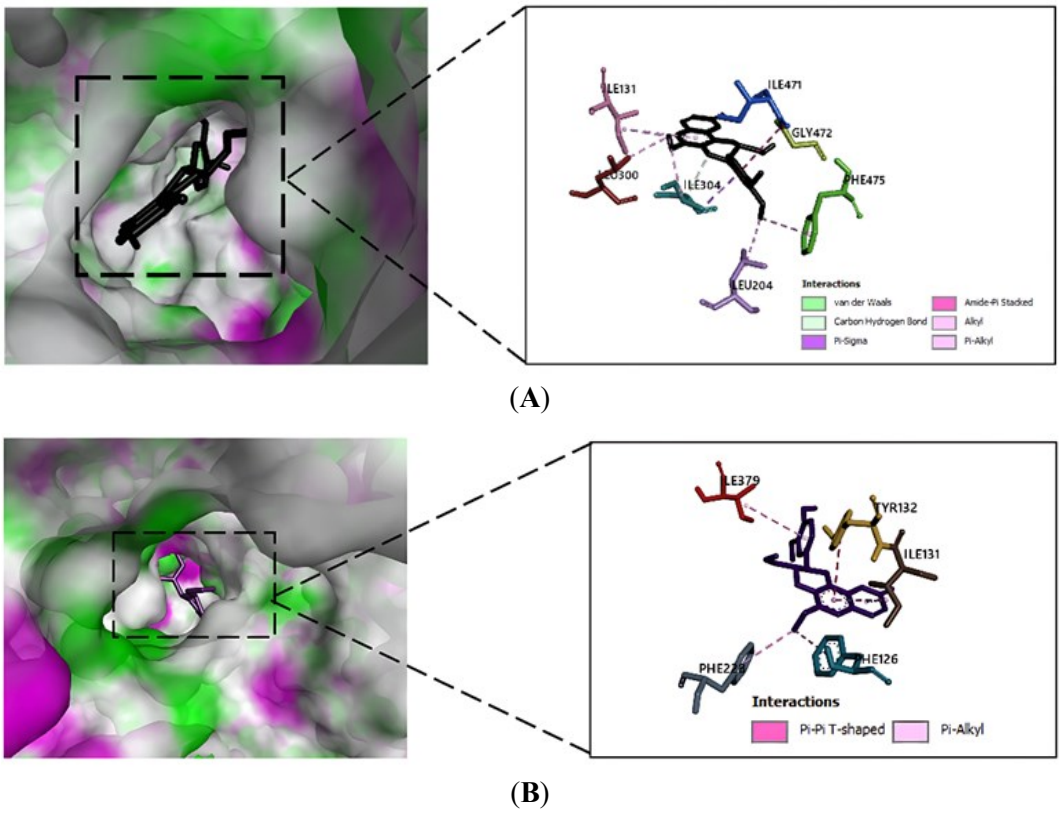
Figure 6. 3D visualization of protein-ligand interactions: (A) SAP6-cleomiscosin A and (B) SAP6-epicatechin.



(**A**) (**B**)

Figure 7. 2D visualization of protein-ligand interactions: (A) ERG11-cleomiscosin A and (B) ERG11-cleomiscosin B.



(**A**)

(**B**)

Figure 8. 3D visualization of protein-ligand interactions: (A) ERG11-cleomiscosin A and (B) ERG11-cleomiscosin B.

For ERG11, the interaction with cleomiscosin A involves the amino acid residues Ile131, Leu200, Leu204, Ile304, Thr311, and Phe475 (Figures 7 (A) and 8 (A)). The residues involved in the interaction of ERG11 with Cleomiscosin B are Phe126, Ile131, Tyr132, Phe228, and Ile379 (Figures 7 (B) and 8 (B)). The residue Ile131 is common to both interactions, highlighting its pivotal role in ligand binding [25][26]. This residue could be prioritized for ligand modifications to increase efficacy and selectivity against ERG11 [27].

Catechin, epicatechin, cleomiscosin A, and

cleomiscosin B belong to the flavonoid and coumarin groups. Previous studies by Susilawati et al. [26] and Xu et al. [27] have demonstrated the effectiveness of flavonoids and coumarins in inhibiting *C. albicans* growth, even when compared to conventional treatments. Flavonoids inhibit *C. albicans* growth and proliferation by disrupting cell walls, membranes, mitochondria, and cell division, while coumarins induce apoptosis and disrupt mitochondrial function, as shown in both *in-vitro* and *in-vivo* studies. Cleomiscosins A and B also interact with ERG11, involving residues Phe126, Ile131, Tyr132, Phe228, and Ile379, confirming their action on ERG11's catalytic residues. This allows them to compete with natural substrates for the active site, potentially acting as competitive inhibitors [25]. Coumarins are known to inhibit lanosterol 14-α demethylase, the enzyme encoded by ERG11, disrupting ergosterol synthesis and leading to fungal cell death [27].

3.3. Molecular Dynamics

The molecular dynamics (MD) simulations were conducted over a 10-ns timescale using OpenMM to investigate the stability and structural flexibility of SAP4-catechin, SAP5-cleomiscosin B, SAP6-cleomiscosin A, and ERG11-cleomiscosin A complexes, as shown in Fig. 9. The RMSD plots (blue graphs, left column) demonstrate varying levels of structural stability across the complexes. SAP4-catechin (panel A) and SAP5-cleomiscosin B (panel B) exhibited stable RMSD values around 2.0–2.5 Å, indicating minimal conformational changes after initial equilibration and suggesting robust protein-

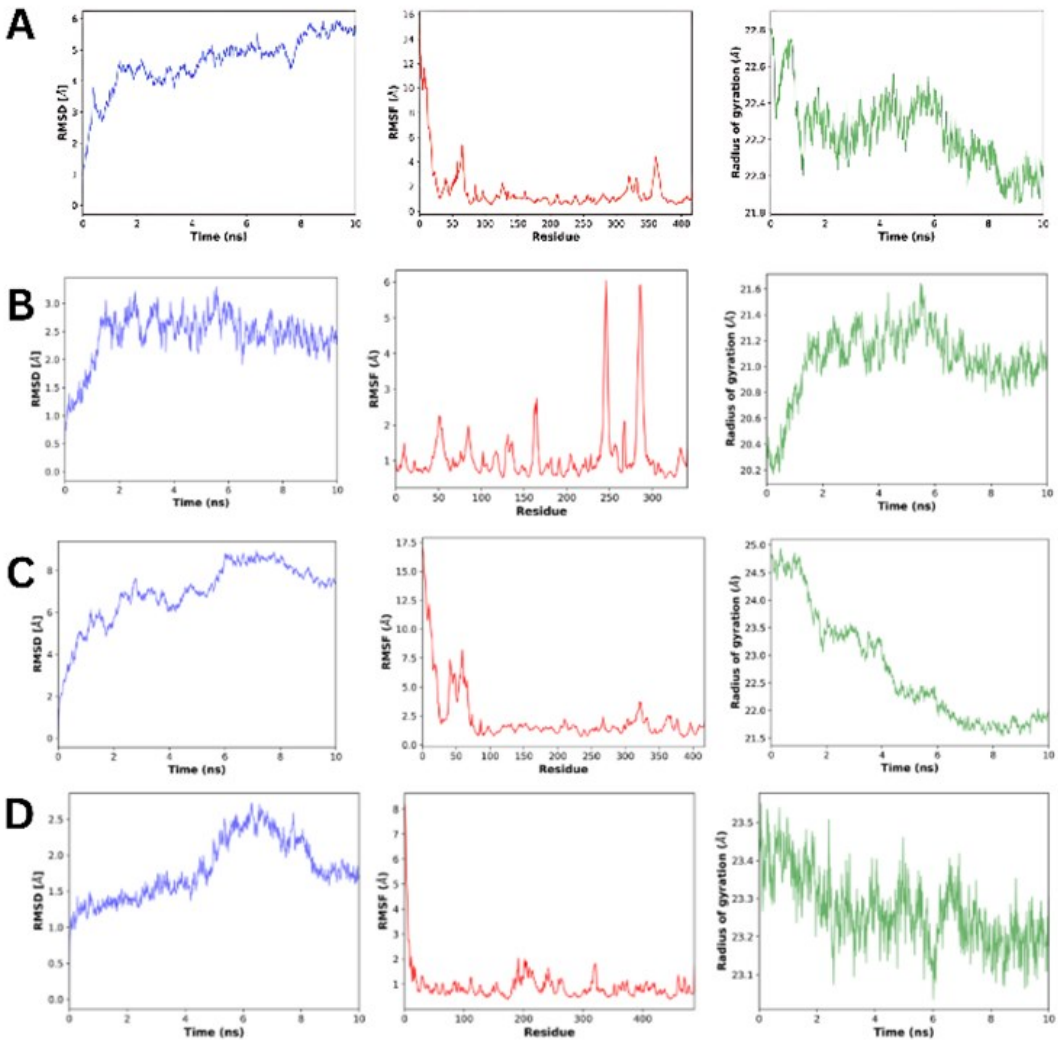


Figure 9. Plots of RMSD, RMSF, and Rg for (A) SAP4-catechin, (B) SAP5-clemiscosin B, (C) SAP6-clemiscosin A, and (D) ERG11-cleomiscosin A.

ligand interactions. In contrast, SAP6-cleomiscosin A (panel C) and ERG11-cleomiscosin A (panel D) showed higher RMSD values (~3.5 Å), suggesting greater structural adjustments during the simulation. The RMSF analysis (red graphs, middle column) revealed the residue-level flexibility, with SAP4-catechin and SAP5-cleomiscosin B showing moderate fluctuations (2–4 Å), indicating stable protein structures with localized flexibility. Meanwhile, SAP6-cleomiscosin A and ERG11-cleomiscosin A demonstrated more pronounced peaks exceeding 5 Å, suggesting higher flexibility in regions potentially involved in ligand binding. The radius of gyration (Rg) plots (green graphs, right column) provided insights into structural compactness. SAP4-catechin and SAP5-cleomiscosin B maintained consistent Rg values (21.6–22.0 Å), indicating well-maintained compact structures. In contrast, SAP6-cleomiscosin A and ERG11-cleomiscosin A showed higher Rg values (34.6–34.8 Å), suggesting more open conformations or larger structural arrangements, while still maintaining overall structural integrity throughout the simulation period.

3.4. Pharmacokinetics and Toxicity Analysis of Durian Rind Compounds

Pharmacokinetics and toxicity analysis are processes used to understand and identify the characteristics of a drug within the body and the potential adverse effects of the drug candidate. Several pharmacokinetic parameters evaluated in this analysis include absorption, distribution, metabolism, and excretion. For toxicity, parameters such as Oral Rat Chronic Toxicity (LOAEL), hepatotoxicity, and skin sensitization were assessed. In this study, pharmacokinetics and toxicity analyses were conducted online using the pkCSM tool. The results of these analyses provide valuable insights into the safety and efficacy profiles of the durian rind compounds. The detailed results of the pharmacokinetics and toxicity evaluations are presented in Table 4.

In Table 4, the absorption parameters observed include water solubility, Caco2 permeability, intestinal absorption, and skin permeability. The water solubility values of all compounds were relatively lower than the control compound, with the lowest value observed in cleomiscosin B (-4.135)

Table 4. Results of pharmacokinetics and toxicity analysis of durian rind compounds.

Compounds	Absorption				Distribution
	Water solubility	Caco-2 permeability	Intestinal absorption (human)	Skin Permeability	VDss (human)
Cleomiscosin B	-4.135	1.214	95.758	-2.737	-0.032
Cleomiscosin A	-3.848	1.239	100.00	-2.735	-0.012
Fraxidin	-2.896	1.345	95.603	-2.906	-0.089
Sinapic Acid	-2.814	0.223	94.503	-2.732	-1.038
Quercitin	-2.982	0.694	74.840	-2.735	0.310
Cathecin	-3.024	-0.410	72.539	-2.735	0.589
Epicatechin	-3.024	-0.410	72.539	-2.735	0.589
Fraxetin	-2.565	1.309	81.035	-3.104	0.118
Fluconazole*	-2.755	1.385	81.521	-2.736	-0.404

*Control

Table 5. Results of pharmacokinetics and toxicity analysis of durian rind compounds.

Compounds	Metabolism				Excretion	Toxicity		
	CYP2D6 substrate	CYP3A4 substrate	CYP2D6 inhibitior	CYP3A4 inhibitior	Total Clearance	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepato toxicity	Skin Sensitisation
Cleomiscosin B	No	No	No	Yes	0.489	2.378	2.349	No	No
Cleomiscosin A	No	No	No	Yes	0.514	2.509	2.317	No	No
Fraxidin	No	No	No	No	0.764	2.095	2.496	No	No
Sinapic Acid	No	No	No	No	0.770	1.877	2.301	No	No
Quercitin	No	No	No	No	0.624	2.308	3.134	No	No
Cathecin	No	No	No	No	0.286	2.011	2.919	No	No
Epicatechin	No	No	No	No	0.286	2.011	2.919	No	No
Fraxetin	No	No	No	No	0.707	1.947	2.342	No	No
Fluconazole*	No	Yes	No	No	0.465	2.384	1.006	Yes	No

*Control

and the highest in fraxetin (-2.565). This indicates that all tested compounds tend to be less water-soluble [28]. Additionally, the results showed that the Caco2 permeability value was highest for fraxidin (1.345), although it did not surpass the control compound. Some compounds, such as sinapic acid, quercetin, catechin, and epicatechin, exhibited lower permeability values, indicating poor gastrointestinal absorption and potentially low oral bioavailability [28]. On the other hand, the intestinal absorption values for all compounds were above 30%, signifying good absorption in the intestinal lumen [29]. Regarding skin permeability, all compounds had log Kp values of <-2.5, indicating good skin permeability.

The distribution parameter examined was the volume of distribution at a steady state (VDss). The results indicated that all compounds showed very low distribution, remaining predominantly in plasma, suggesting limited bioavailability in tissues. Sinapic acid had the lowest VDss value (-1.038), indicating poor distribution and a tendency to remain in the bloodstream with minimal tissue distribution [29]. This suggests that the compound is likely more polar or has low tissue affinity. The highest VDss values were observed in catechin and epicatechin, both at 0.589, indicating broader distribution to tissues compared to other compounds, but still not achieving full systemic distribution. Compounds with these values are typically balanced between lipophilic and hydrophilic properties.

The metabolism parameter prediction included the ability of durian rind compounds to act as inhibitors or substrates of CYP2D6 and CYP3A4 enzymes. Cleomiscosins A and B were shown to inhibit CYP2D6 and CYP3A4 and were not substrates for these enzymes, suggesting that these compounds would not hinder the enzymes' functions or be metabolized by the CYP450 system's isoforms CYP2D6 and CYP3A4. Conversely, the control compound was a substrate for CYP3A4, indicating that it would be metabolized by the CYP450 system's 3A4 isoform. The excretion component measured drug clearance (CLtotal), which reflects the combination of hepatic clearance (metabolism in the liver and biliary clearance) and renal clearance (excretion via the kidneys). Sinapic acid had the highest total clearance, suggesting it is excreted from the body the fastest [30]. The final parameter tested

was toxicity, including rat LD_{50}, rat LOAEL, hepatotoxicity, and skin sensitization. The toxicity profile analysis, as shown in Table 5, revealed that all compounds were safe for topical use and non-toxic to the liver, except for the control compound.

4. CONCLUSIONS

In this study, a comprehensive drug-likeness evaluation of 25 compounds derived from durian rind led to the selection of eight promising candidates for further *in silico* molecular docking analysis. These compounds—cleomiscosin B, quercetin, catechin, epicatechin, cleomiscosin A, fraxidin, sinapic acid, and fraxetin—fulfilled the drug-likeness criteria established by Lipinski, Ghose, Veber, Egan, and Muegge rules, indicating their potential as viable drug candidates. Molecular docking simulations demonstrated that several durian rind compounds exhibited binding affinities comparable to or stronger than the control fluconazole, suggesting enhanced interactions with target proteins. Notably, catechin and epicatechin displayed binding affinities of -7.1 and -6.5 kcal/mol against SAP4, while cleomiscosins A and B showed exceptional binding affinities of -9.1 and -9.2 kcal/mol against SAP5. Additionally, both epicatechin and cleomiscosin A exhibited a binding affinity of -7.3 kcal/mol against SAP6, highlighting their potential to inhibit key proteins involved in the pathogenesis of *C. albicans*. Moreover, cleomiscosins A and B demonstrated lower binding affinities of -8.7 and -8.4 kcal/mol, respectively, against ERG11, suggesting their ability to inhibit this critical enzyme in *C. albicans* pathogenicity. Pharmacokinetic analyses further supported their therapeutic potential, revealing favorable intestinal absorption, adequate permeability for systemic distribution, and efficient tissue penetration. Toxicological assessments indicated no significant risks of acute, chronic, or hepatotoxicity, suggesting that these compounds are safe and may serve as promising candidates for further drug development aimed at combating *C. albicans* infections. These findings underscore the potential of durian rind-derived compounds as novel, effective, and safe therapeutic agents.

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Conflicts of Interest

The authors declare no conflict of interest.

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