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In Silico Evaluation of Bioactive Compounds from *Artocarpus heterophyllus* Leaves as Potential Aromatase Inhibitors for Estrogen Receptor Positive Breast Cancer

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ABSTRACT

Breast cancer remains one of the leading causes of mortality among women worldwide, particularly estrogen receptor positive subtypes that depend on aromatase (CYP19A1) activity for estrogen biosynthesis. This study aims to evaluate phytochemical compounds isolated from *Artocarpus heterophyllus* leaves as potential natural aromatase inhibitors using an integrated in silico approach. A total of ten reported secondary metabolites were analyzed alongside Letrozole as a reference inhibitor. Molecular docking was performed against human aromatase (PDB ID: 4GL7) using MOE 2019, and protocol validation was confirmed by redocking of the native ligand with RMSD values below 2.0 Å. The results show that 3 prenyl luteolin, prenyl caffeate, and artocarpanone exhibited strong binding affinities of -7.7958, -7.0193, and -6.9688 kcal/mol, respectively, exceeding that of Letrozole (-6.8069 kcal/mol), with stable docking conformations. Drug likeness evaluation indicates that all tested compounds comply with Lipinski and Veber rules, present acceptable polar surface area, limited rotatable bonds, and a bioavailability score of 0.55. ADMET prediction reveals high gastrointestinal absorption, moderate distribution, controlled clearance, and low toxicity risk, with no predicted AMES mutagenicity or hepatotoxicity for most compounds. These findings suggest that *A. heterophyllus* contains promising bioactive metabolites with favorable binding characteristics and pharmacokinetic profiles, supporting their potential as lead candidates for the development of safer, plant derived aromatase inhibitors for estrogen dependent breast cancer therapy.

Keywords: Artocarpus heterophyllus; Breast cancer; Phytochemicals; Molecular docking; ADMET; Drug-likeness.

INTRODUCTION

In recent years, natural products derived from medicinal plants have gained increasing attention as potential sources of novel therapeutic agents. Compared with synthetic compounds, plant-derived metabolites often exhibit greater structural diversity and a tendency toward lower toxicity, making them attractive candidates for drug discovery and development. The genus Artocarpus (Moraceae) is particularly well recognized for its rich phytochemical composition, including flavonoids, prenylated flavonoids, stilbenoids, and arylbenzofuran derivatives, many of which have been reported to possess antioxidant, cytotoxic, anti-inflammatory, and enzyme-inhibitory activities [6-7].

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.24036/sainstek/ vol4-iss02/59

These biological properties suggest that Artocarpus species may represent valuable natural sources of compounds capable of modulating cancer-related molecular targets.

Among the species within this genus, Artocarpus heterophyllus has been extensively studied for its diverse secondary metabolites and broad pharmacological potential. Several compounds isolated from its leaves have demonstrated cytotoxic and enzyme-inhibitory activities, indicating their relevance to cancer-associated pathways. However, despite the growing body of phytochemical and biological evidence, systematic investigations focusing on the interaction between A. heterophyllus leaf metabolites and aromatase at the molecular level remain scarce. In particular, comprehensive in silico evaluations that integrate binding affinity analysis, interaction profiling, and pharmacokinetic assessment are still limited, leaving an important research gap in understanding the therapeutic relevance of this plant as a source of aromatase inhibitors [8].

In silico approaches, such as molecular docking and ADMET prediction, provide a robust and cost-effective framework for early-stage drug discovery by enabling the evaluation of ligand-protein interactions, binding stability, and pharmacokinetic behavior prior to experimental validation. These computational methods allow for the rapid screening and prioritization of candidate compounds, thereby reducing time and resource requirements associated with in vitro and in vivo studies [9-10]. Moreover, integrated in silico strategies facilitate the identification of structural features that contribute to favorable binding and drug-likeness properties, supporting rational lead optimization in subsequent development stages [11].

Based on this rationale, the present study aims to evaluate ten phytochemical compounds previously isolated from Artocarpus heterophyllus leaves as potential aromatase inhibitors using an integrated in silico approach, with letrozole employed as a reference standard. By systematically analyzing binding affinity, interaction patterns within the aromatase active site, and pharmacokinetic characteristics, this study seeks to elucidate the molecular basis of aromatase inhibition by A. heterophyllus metabolites. The findings are expected to contribute to a deeper chemopharmacological understanding of this plant and to identify promising natural lead compounds that may support the development of safer and more effective therapeutic alternatives for estrogen-dependent breast cancer [12-13].

METHOD

Protein Preparation

The three-dimensional crystal structure of human aromatase (CYP19A1) was obtained from the Protein Data Bank (PDB ID: 4GL7). Protein preparation was performed using the QuickPrep module implemented in Molecular Operating Environment (MOE). All crystallographic water molecules, co-crystallized ligands, and non-essential ions were removed. The QuickPrep workflow automatically added hydrogen atoms, assigned appropriate protonation states at physiological pH, corrected structural imperfections, and conducted energy minimization using the AMBER10 force field, yielding a stable protein conformation suitable for docking studies.

Ligand Preparation

Ten phytochemical compounds isolated from Artocarpus heterophyllus leaves, namely artocarpin, 3-prenyl luteolin, cycloartocarpin, isoartocarpesin, cintriamide, dihydromorin, albanin A, cycloheterophyllin, artocarpanone, and prenyl caffeate, were selected as test ligands, with letrozole employed as a positive control. Ligand structures were retrieved from the PubChem database in the form of SMILES codes and imported into MOE. Each ligand was converted into a three-dimensional structure, protonated under physiological pH conditions, and subjected to energy minimization using the AMBER10 force field to ensure force field consistency with the prepared protein.

Molecular Docking

Molecular docking was carried out using MOE. The active site of aromatase was defined based on the binding cavity corresponding to the native ligand position in the original 4GL7 crystal structure. Docking was conducted using the Triangle Matcher placement method. Initial pose scoring was performed using the London dG scoring function, followed by refinement through force field-based energy minimization. Final binding affinities were calculated using the GBVI/WSA dG scoring function, and the docking score (S-score,

kcal/mol) of each ligand was recorded. For each ligand, the top-ranked pose with the lowest S-score and appropriate binding orientation was selected for further analysis.

Docking Validation

The docking protocol was validated by redocking the native ligand extracted from the 4GL7 structure into the prepared aromatase binding site using identical docking parameters. The accuracy of the docking procedure was evaluated by calculating the root-mean-square deviation (RMSD) between the redocked ligand pose and the original crystallographic conformation. An RMSD value of ≤ 2.0 Å was considered indicative of a reliable and reproducible docking protocol.

Interaction Analysis

Protein-ligand interaction analysis was performed using BIOVIA Discovery Studio Visualizer. Key interactions, including hydrogen bonds, hydrophobic contacts, pi-pi stacking, and electrostatic interactions, were identified and visualized. The interaction profiles were correlated with docking S-scores and RMSD values to assess binding stability and ligand orientation within the active site.

Drug-Likeness and ADMET Prediction

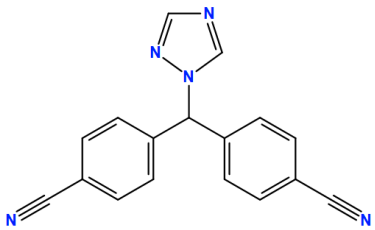
Drug-likeness properties were evaluated using SwissADME based on Lipinski's Rule of Five and Veber criteria. Pharmacokinetic and toxicity profiles were predicted using SwissADME, pkCSM, and ADMETlab 2.0, including gastrointestinal absorption, CYP450 enzyme inhibition, bioavailability, hepatotoxicity, and mutagenicity.

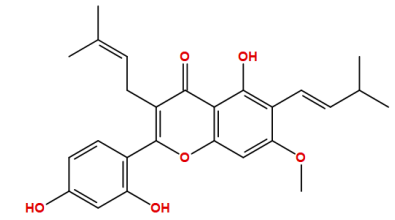
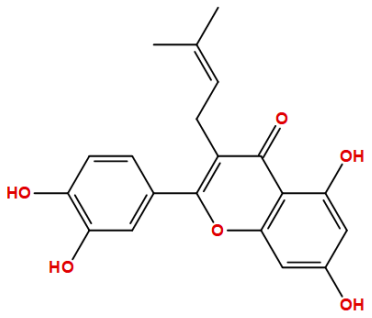
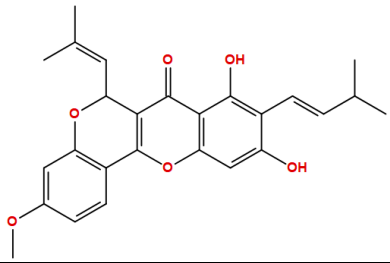
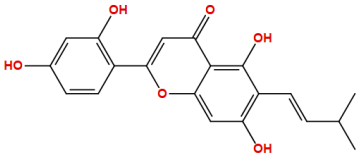
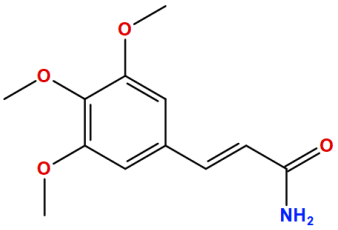
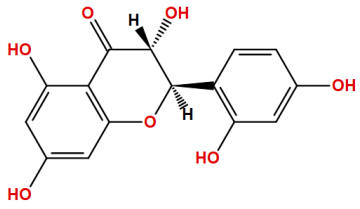
RESULTS AND DISCUSSION

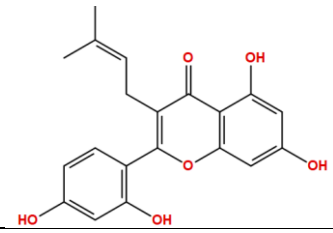
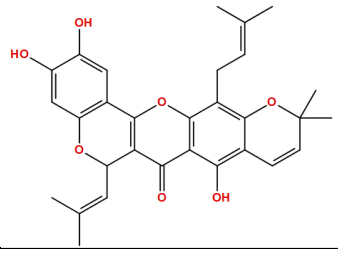
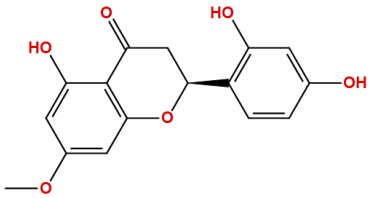
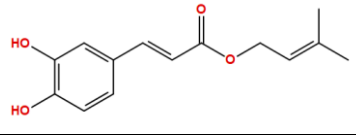
The table of tested compounds derived from Artocarpus heterophyllus leaves demonstrates that this plant contains a diverse range of secondary metabolites, including flavonoids, prenylated flavones, phenolics, and triterpenoids. This phytochemical diversity suggests a potential therapeutic relevance of A. heterophyllus, particularly in estrogen-dependent breast cancer therapy. Flavonoid derivatives such as artocarpin, 3-prenyl luteolin, cycloartocarpin, isoartocarpesin, and dihydromorin have been widely reported to exhibit antiproliferative, antioxidant, and enzyme-inhibitory activities that may suppress the estrogen biosynthesis pathway by targeting aromatase [14]. Phenolic compounds like prenyl caffeate also contribute through strong polar interactions and high redox activity, while highly hydrophobic prenylated compounds such as albanin A and cycloheterophyllin provide additional stabilizing hydrophobic interactions within the catalytic site of the aromatase enzyme.

The inclusion of Letrozole as a positive control provides a clinically validated reference point, as this synthetic aromatase inhibitor is widely used in the management of hormone-dependent breast cancer [15]. By comparing the docking interactions and binding energies of A. heterophyllus metabolites with those of Letrozole, the table highlights that this plant contains pharmacologically relevant compounds that may serve as promising natural candidates for the development of safer and effective aromatase inhibitors for breast cancer therapy.

Table 1. Test compounds contained in the sample *Artocarpus heterophyllus*

No	Compound Name	Structure	Reference
1	Letrozole (Positive Control)		[16]
2	Artocarpin		[17]

No	Compound Name	Structure	Reference
			
3	3-prenyl luteolin		[18]
4	Cycloartocarpin		[19]
5	Isoartocarpesin		[20]
6	Cintriamide		[21]
7	Dihydromorin		[22]

No	Compound Name	Structure	Reference
8	Albanin A		[23]
9	Cycloheterophyllin		[24]
10	Artocarpanone		[25]
11	Prenyl Caffeate		[26]

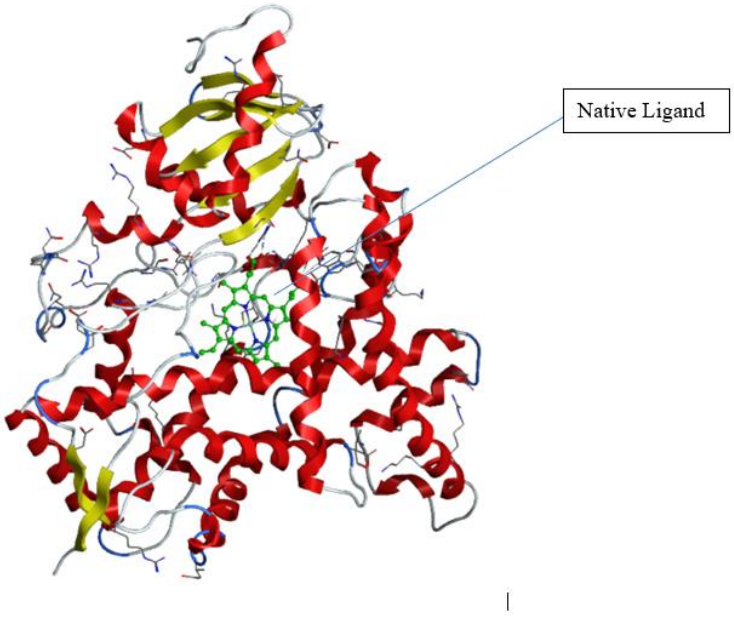


Figure 1. Surface Torpology of Protein 4GL7

Figure 1 presents the surface topology of the aromatase enzyme (PDB ID: 4GL7), providing a detailed visualization of the overall three-dimensional architecture of its catalytic binding pocket. The surface representation highlights the grooves, cavities, and structural contours that shape the ligand-accessible regions of the enzyme. These features reveal a well-organized distribution of hydrophobic cores, polar regions, and hydrogen-bonding hotspots, all of which play essential roles in ligand accommodation and molecular recognition. The clearly defined topology of the binding pocket indicates how the enzyme structurally supports the stabilization of ligands, particularly through orientation-specific interactions that are facilitated by the spatial arrangement of surrounding residues. This structural visualization is important for understanding how aromatase accommodates ligands involved in estrogen biosynthesis, as the geometry and physicochemical properties of the binding pocket determine ligand complementarity, binding affinity, and potential inhibitory activity. Overall, Figure 1 provides a foundational structural perspective that supports subsequent analyses of ligand interactions and helps validate the molecular docking approach using aromatase (4GL7) as a reliable target model.

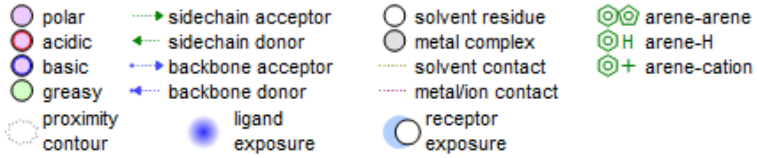
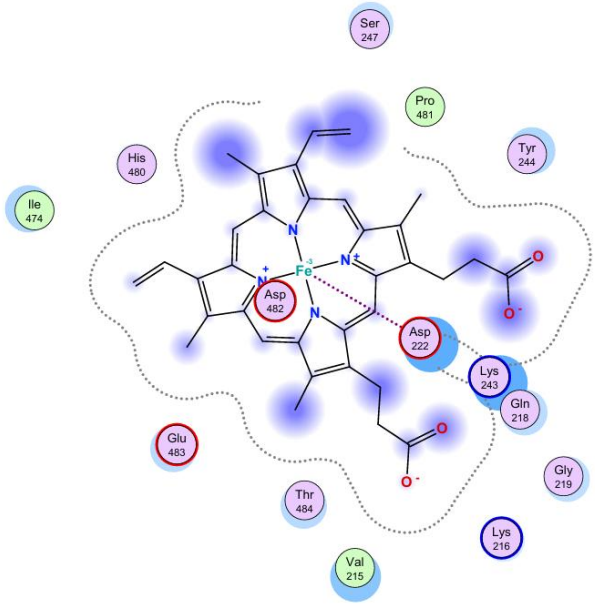


Figure 2. Native Ligand Interaction on Protein 4GL7 (Concise Version)

Figure 2 illustrates the interaction profile between the native ligand and the active site of protein 4GL7, showing the ligand positioned at the center of the binding pocket and surrounded by amino acid residues that stabilize the complex through key non-covalent contacts such as hydrogen bonds, aromatic interactions, and hydrophobic contacts. Polar residues like Ser, Thr, and Asn act as hydrogen-bond donors or acceptors, helping maintain ligand orientation, while aromatic residues such as Phe and Tyr form arene-H or arene-arene interactions that enhance complex stability through π-type contacts. Hydrophobic residues including Leu, Val, and Ile pack around the ligand's non-polar regions, adding further stabilization, and the presence of basic and acidic residues contributes to an electrostatically supportive environment. Altogether, this combination of interactions demonstrates that the native ligand binds optimally within the active site of protein 4GL7, reflecting strong binding affinity and highlighting its functional relevance in the protein's biological activity.



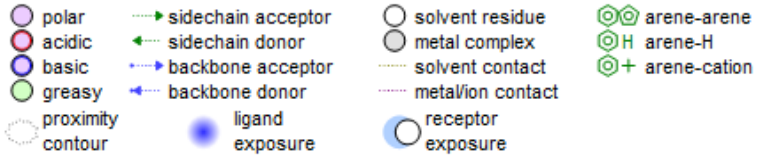


Figure 3. Visualization of the Redocked Ligand in the Protein Binding Pocket

Figure 3 illustrates the redocking visualization of the native ligand within the binding pocket of the aromatase enzyme (PDB ID: 4GL7), demonstrating how the redocked pose aligns accurately with the original crystallographic binding orientation. The visualization confirms that the ligand successfully reoccupies the same catalytic cavity and maintains key interactions with the amino acid residues responsible for stabilizing the native complex, indicating that the docking grid and parameter settings were appropriately defined. This depiction is essential for validating the structural accuracy of the docking procedure, as a correctly repositioned ligand reflects sufficient search-space coverage and precise mapping of the active-site coordinates. Such consistency between the crystallographic and predicted poses further supports the reliability of the docking simulation for evaluating the binding behavior of the *Artocarpus heterophyllus* phytochemicals.

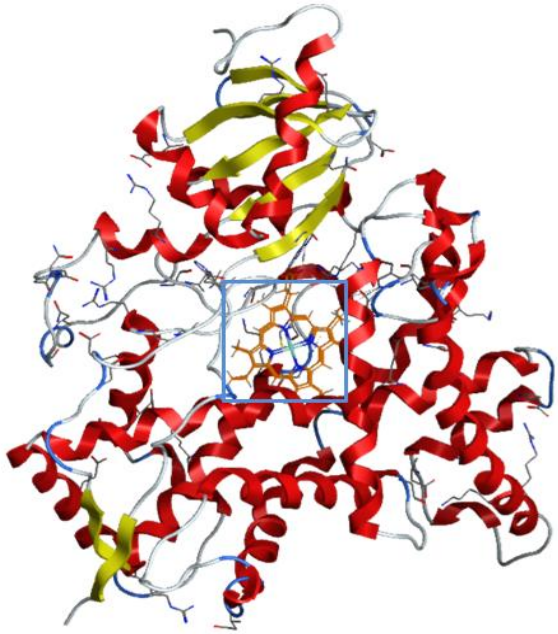
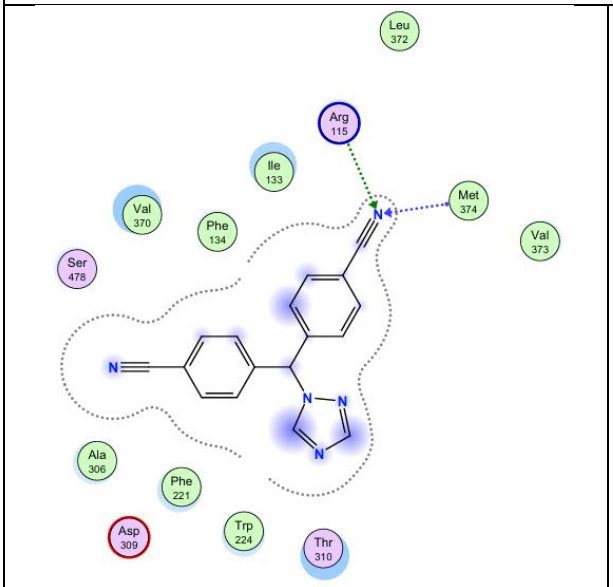
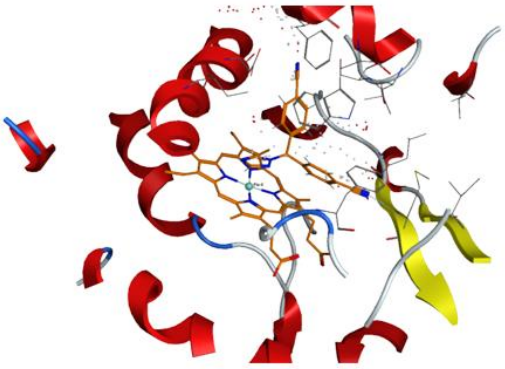


Figure 4. Overlay of the Crystallized Ligand and the Redocked Ligand

Figure 4 presents the overlay between the crystallographic ligand and the redocked ligand, showing the high degree of similarity between the experimental and predicted conformations. The close alignment of both ligand poses reflects a low RMSD value, indicating strong accuracy and reliability of the docking protocol. This structural agreement confirms that MOE 2019 successfully reproduces the native binding orientation within the aromatase active site, thereby strengthening the credibility of the docking results obtained for the *Artocarpus heterophyllus* phytochemicals. Collectively, Figures 3 and 4 validate that the docking procedure is robust and appropriate for predicting the interaction patterns and inhibitory potential of the test compounds against the aromatase enzyme.

Table 2. Binding Interactions of the compound (A) Letrozole, (B) Artocarpin, (C) 3-prenyl luteolin, (D) Cycloartocarpin, (E) Isoartocarpesin, (F) Cintriamide, (G) Dihydromorin, (H) Albanin A, (I) Cycloheterophyllin, (J) Artocarpanone, (K) Prenyl Caffeate.

Ligan Interaction	Protein
A	
	
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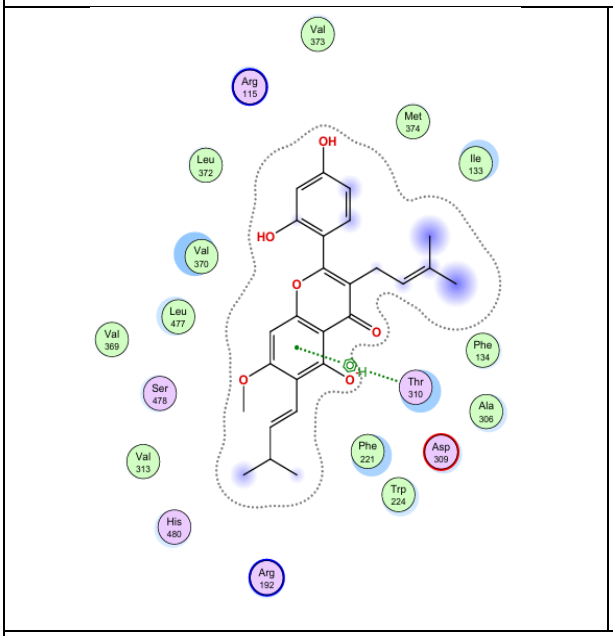
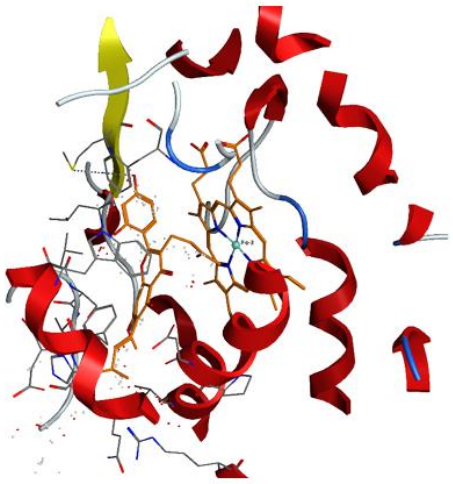
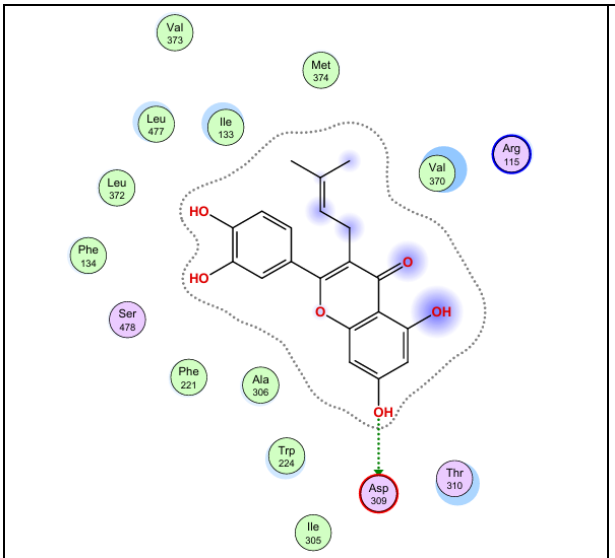
	
C	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Arg 115
Val 370
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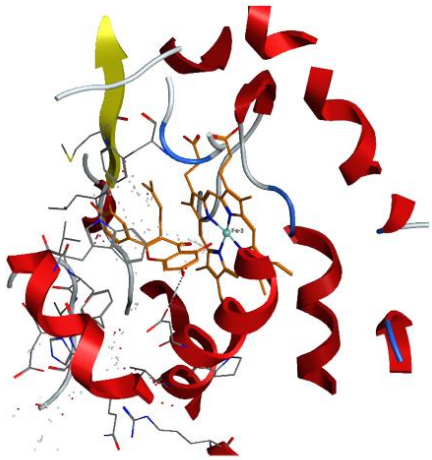
Ile 305



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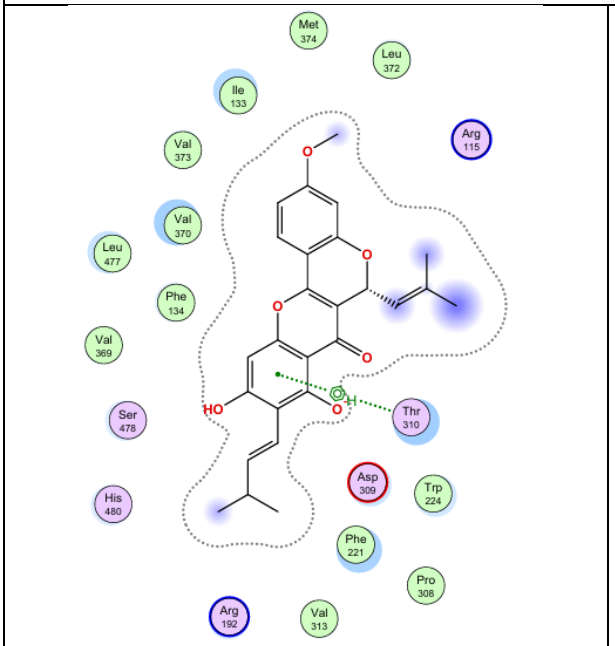
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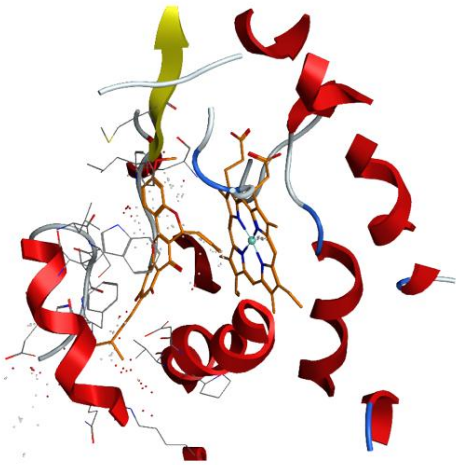

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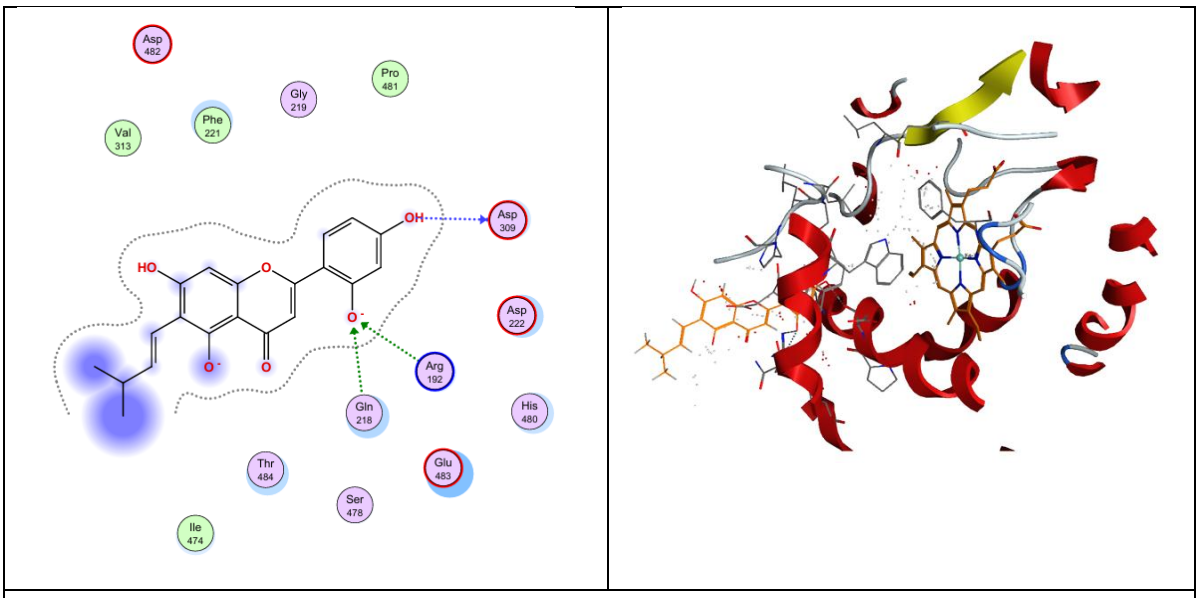
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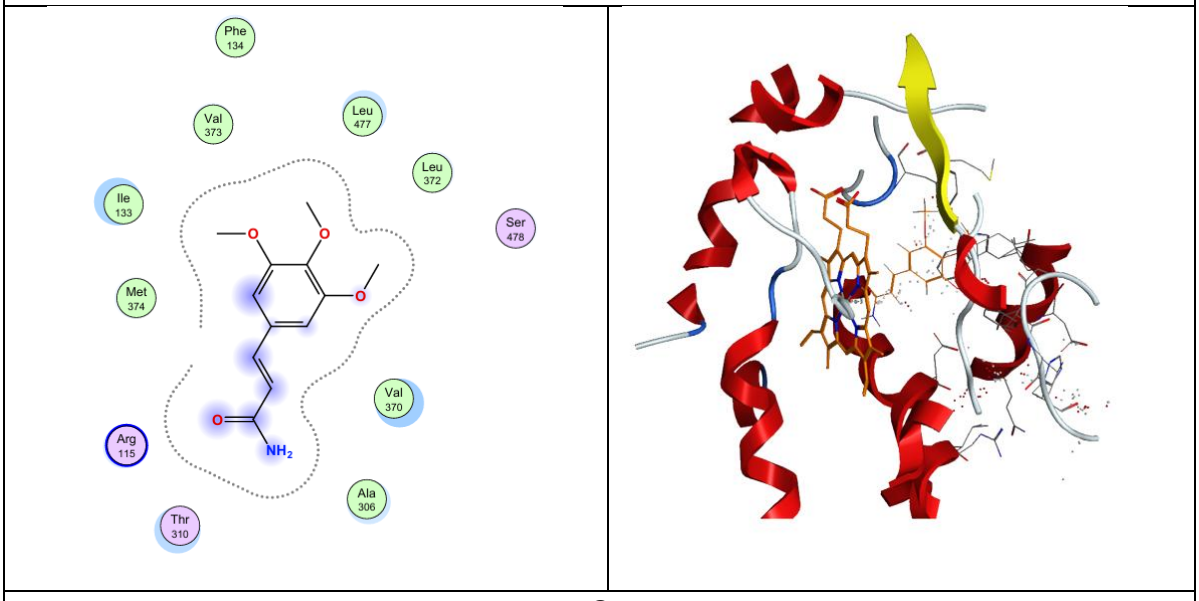
F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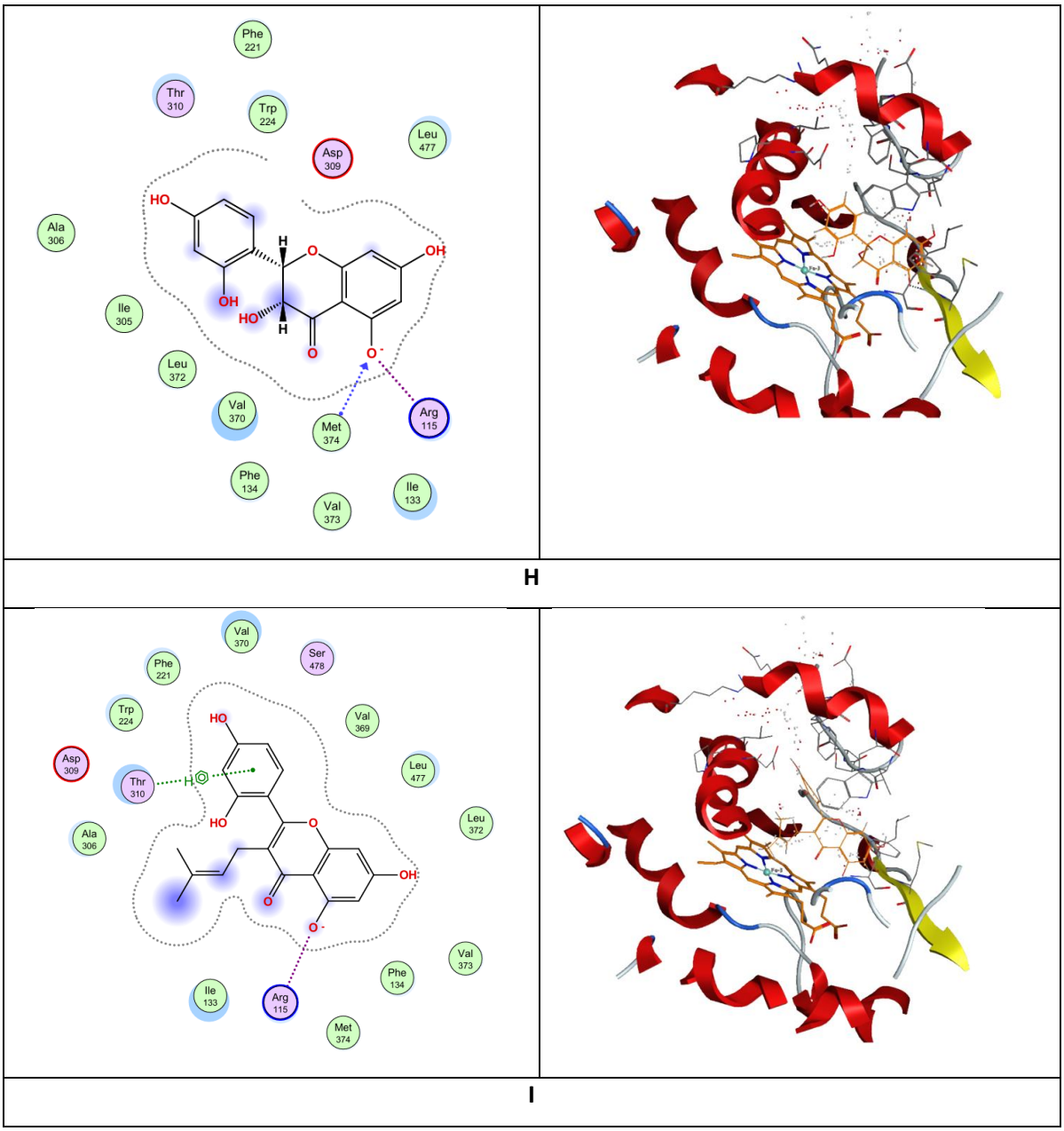
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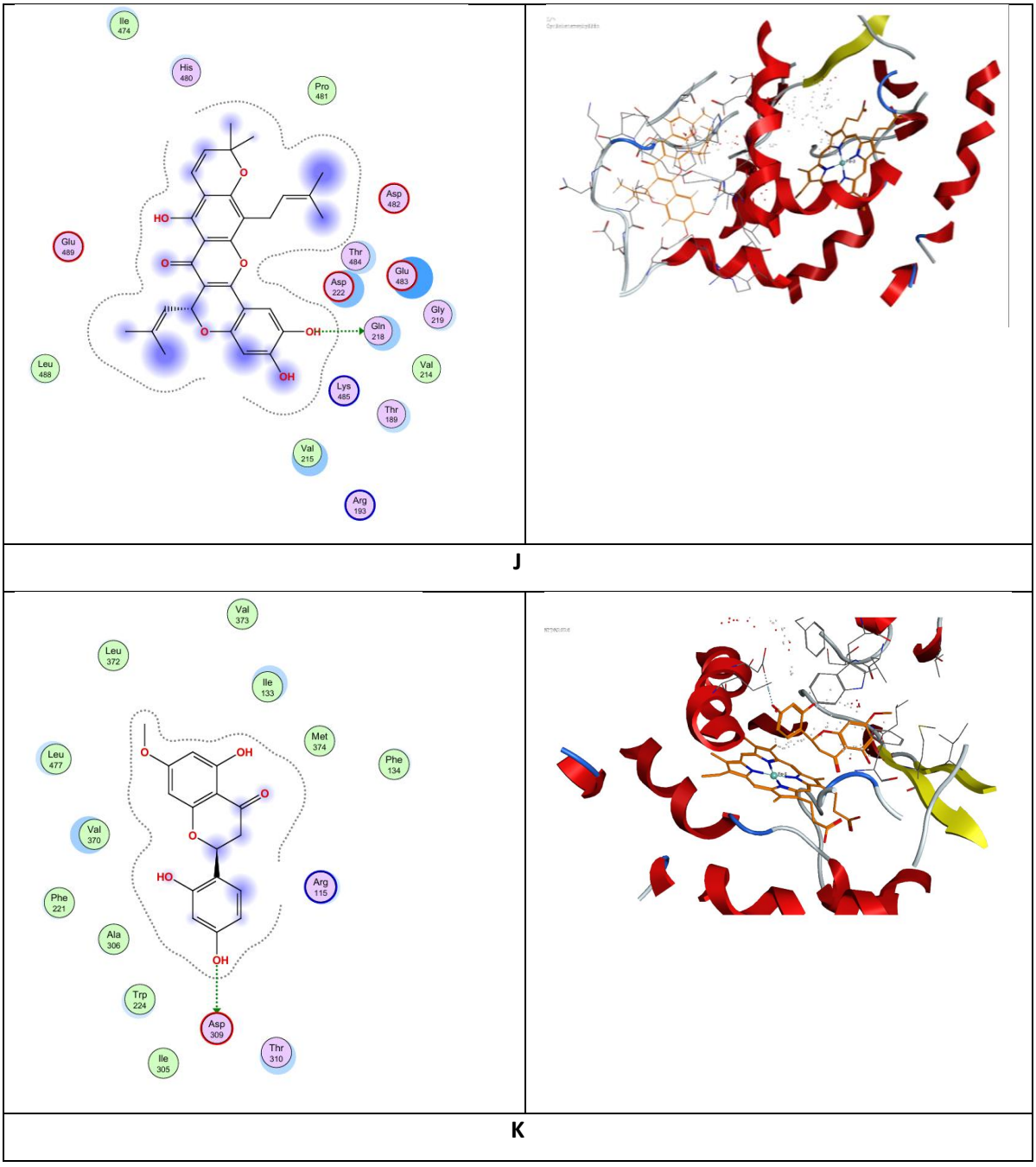
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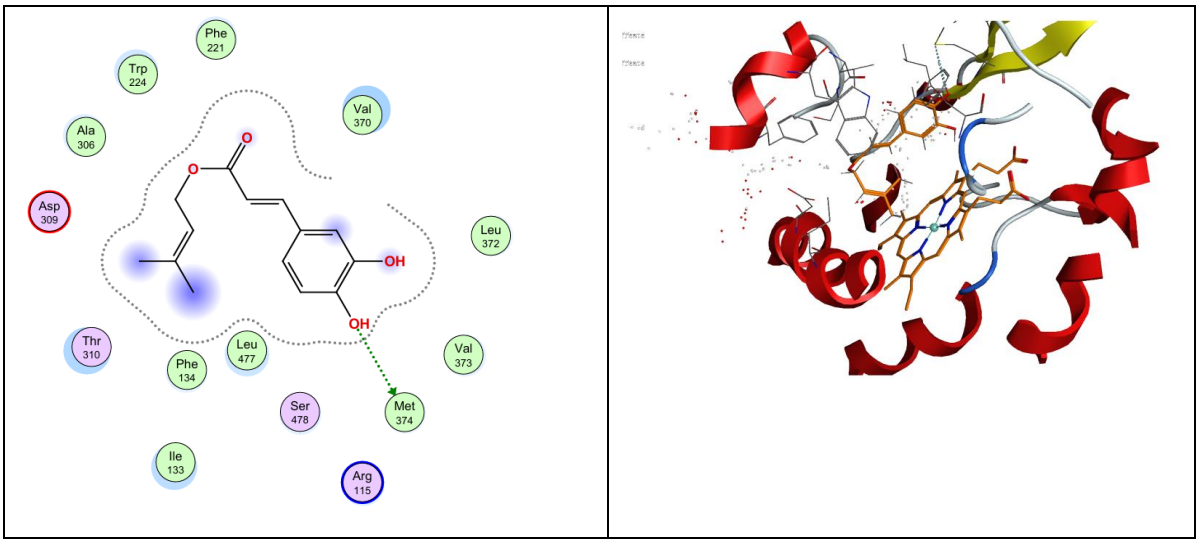

Table 2 summarizes the binding interactions formed between the aromatase enzyme (PDB ID: 4GL7) and the eleven tested ligands, including the reference drug Letrozole and ten phytochemical compounds derived from *Artocarpus heterophyllus*. Letrozole, used as the standard aromatase inhibitor in clinical breast cancer therapy, demonstrates strong and well-defined interactions within the active binding pocket, serving as a benchmark for evaluating the docking performance of the plant-derived compounds. Several natural compounds particularly 3-prenyl luteolin, prenyl caffeate, artocarpanone, and artocarpin exhibit comparable or, in some cases, more extensive interaction profiles, forming hydrogen bonds, aromatic contacts, and hydrophobic interactions with key catalytic residues that stabilize the ligand-protein complex. These interaction patterns indicate that structurally diverse phytochemicals are capable of effectively occupying the active site and potentially modulating aromatase activity. Compounds such as dihydromorin and isoartocarpesin also demonstrate favorable polar and hydrogen-bond interactions, reflecting their ability to achieve strong affinity through hydroxyl-rich functional groups. Meanwhile, highly hydrophobic prenylated compounds such as albanin A contribute primarily through hydrophobic contacts that enhance pocket stabilization. Overall, the interaction profiles presented in Table 2 highlight that several *A. heterophyllus* constituents possess promising binding characteristics that mirror, and in some cases approach, the interaction behavior of the standard ligand Letrozole, supporting their potential as natural aromatase inhibitors.

Tabel 3. Docking Score (S) and RMSD Value of Test Compound and Letrozole againts 4GL7

No	Compound Name	Docking Score (S) (kcal.mol^{-1})	RMSD
1.	Letrozole (Kontrol positif)	-6.8069	1.0109
2.	Artocarpin	-6.1398	1.2177
3.	3-prenyl luteolin	-7.7958	1.3226
4.	Cycloartocarpin	-5.1566	0.9652
5.	Isoartocarpesin	-5.6142	1.1105
6.	Cintriamide	-6.5045	0.7613
7.	Dihydromorin	-6.1953	0.8149
8.	Albanin A	-6.2221	1.0258
9.	Cycloheterophyllin	-6.2504	1.2121
10.	Artocarpanone	-6.9688	1.0875
11.	Prenyl Caffeate	-7.0193	0.8507

The molecular docking results presented in Table 3 indicate that several phytochemical compounds from *Artocarpus heterophyllus* exhibit strong interaction potential with the aromatase enzyme (PDB ID: 4GL7). Compounds such as 3-prenyl luteolin, prenyl caffeate, and artocarpanone display notably low (more negative) docking scores, suggesting stronger and more stable binding affinities compared to the other tested ligands. Remarkably, the docking score of 3-prenyl luteolin surpasses that of the reference drug Letrozole, suggesting a potentially stronger binding affinity toward the aromatase active site. Although other compounds such as artocarpin, dihydromorin, and cycloheterophyllin show slightly higher docking scores, they still demonstrate meaningful interaction potential

based on their stable positioning within the catalytic pocket. Furthermore, all ligands exhibit RMSD values ≤ 2 Å, confirming that the predicted docking poses are stable and reliable, and accurately represent ligand-protein interactions. These findings collectively suggest that several *A. heterophyllus* metabolites possess promising inhibitory characteristics that warrant further investigation as natural aromatase inhibitors.

Tabel 4. Drug-likeness Evaluation of Artocarpus Heterophyllus Compounds

No	Compound Name	Lipinski Ro5				Veber		*Bioavailability Score*	Probabel
		H-Donor (<5)	H-*Acceptor* (<10)	Log P (<5)	Mw (g/mol) (<500)	*Rotatable Bonds* (≤ 10)	PSA Å (<140)		
1.	Artocarpin	3	6	5,7633	436,50	6	100,13	0,55	*Drug-like molecule*
2.	3-prenyl luteolin	4	6	3,7911	354,35	3	111,13	0,55	*Drug-like molecule*
3.	Cycloartocarpin	2	6	5,9487	434,48	4	89,13	0,55	*Drug-like molecule*
4.	Isoartocarpesin	4	6	3,9516	354,35	3	111,13	0,55	*Drug-like molecule*
5.	Cintriamide	1	4	1,2109	237,25	5	70,78	0,55	*Drug-like molecule*
6.	Dihydromorin	5	7	1,1863	304,25	1	127,45	0,55	*Drug-like molecule*
7.	Albanin A	4	6	3,7911	354,35	3	111,13	0,55	*Drug-like molecule*
8.	Cycloheterophyllin	4	7	3,12	340,33	2	104,36	0,55	*Drug-like molecule*
9.	Artocarpanone	2	6	3,78	354,35	4	86,99	0,55	*Drug-like molecule*
10.	Prenyl Caffeate	2	5	3,21	248,28	6	66,76	0,55	*Drug-like molecule*
11.	Letrozole (Control positif)	0	4	2,65916	285,30	3	78,29	0.55	*Drug-like molecule*

The drug-likeness evaluation in Table 4 reveals that all phytochemical compounds from *Artocarpus heterophyllus* comply with Lipinski's Rule of Five, indicating favorable physicochemical characteristics for oral absorption and early-stage drug development. Phenolic and flavonoid derivatives such as artocarpin, 3-prenyl luteolin, isoartocarpesin, dihydromorin, and cycloheterophyllin exhibit acceptable molecular weight, hydrogen-bond capacity, and lipophilicity values, suggesting suitable pharmacokinetic behavior and promising bioavailability. Even compounds with higher hydrophobicity, such as artocarpin and cycloartocarpin, remain within the acceptable limits of drug-likeness criteria, indicating that their prenylated structures do not compromise their pharmacological potential. Likewise, triterpenoid-leaning compounds such as albanin A and prenyl caffeate also meet the required thresholds, demonstrating that structural diversity within the plant does not hinder compliance with drug-likeness parameters. Overall, the consistent fulfillment of Lipinski and Veber rules across all compounds highlights the suitability of *A. heterophyllus* metabolites for further pharmacological optimization and development as potential natural aromatase inhibitors.

Tabel 5 . ADMET Properties of Artocarpus Heterophyllus Compounds

NO	Compound Name	ABSORPTION						DISTRIBUTION		METABOLISM					EXCRETION		TOXICITY				
		GI	Water solubility (log mol/L)	Caco2 permeability (log Papp in 10-6 cm/s)	Intestinal absorption (% Absorbed)	Pgp Substrate	Pgp Inhibitor	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Renal OCT2 (Substrate)	Total Clearance	Toxicity class	Max. tolerated dose (log mg/kg/day)	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Hepatotoxicity	AMES toxicity
1.	Artocarpin	High	-4,174	-0,396	95,222	Yes	Yes	-1,484	0,042	No	Yes	No	No	No	No	0,409	-	-0,01	2,022	Yes	Yes
2.	3-prenyl luteolin	High	-3,196	-0,034	84,027	Yes	No	-0,084	0,017	Yes	No	Yes	Yes	No	No	0,356	-	0,627	2,641	No	No
3.	Cycloartocarpin	High	-4,555	1,171	94,34	Yes	Yes	-0,916	0,056	No	Yes	Yes	No	No	No	0,325	-	0,033	1,939	Yes	No
4.	Isoartocarpesin	High	-3,513	0,773	83,936	Yes	No	-0,38	0	Yes	No	Yes	Yes	No	No	0,37	-	0,63	2,421	No	No
5.	Cintriamide	High	-2,295	0,32	78,534	No	No	-0,307	0,303	No	No	No	No	No	No	0,76	-	0,947	2,075	No	No
6.	Dihydromorin	High	-3,051	-0,3	63,269	Yes	No	0,793	0,205	No	No	No	No	No	No	0,382	-	0,446	1,826	No	No
7.	Albanin A	High	-3,131	-0,013	87,123	Yes	No	-0,046	0,008	Yes	No	Yes	Yes	No	No	0,399	-	0,684	2,662	No	No
8.	Cycloheterophyllin	High	-4.45	0.120	88,7	Yes	No	-0,40	0,048	No	No	No	No	No	No	0,32	-	0,30	1,60	No	No
9.	Artocarpanone	High	-3,18	0,520	9,14	No	No	0,05	0,087	No	No	No	No	No	No	0,25	-	0,45	2,05	No	No
10.	Prenyl Caffeate	High	-3,65	0,810	96,1	No	No	0,12	0,142	No	No	No	No	No	No	0,40	-	0,60	1,95	No	No
11.	Letrozole (Control positif)	High	-3,735	0,901	100	No	No	-0,044	0,203	Yes	Yes	Yes	Yes	No	Yes	0,79	-	-0,018	2,125	No	No

The ADMET evaluation of the compounds derived from *Artocarpus heterophyllus* reveals generally favorable pharmacokinetic characteristics, although a few limitations are observed in certain molecules. In terms of absorption, most compounds exhibit low water solubility; however, their Caco-2 permeability values indicate good membrane penetration. This is supported by the generally high predicted intestinal absorption values; however, artocarpanone shows notably lower absorption compared to the other compounds. Their interactions with P-glycoprotein (P-gp) vary, with some acting as inhibitors that may increase efflux in the intestinal tract, while others do not show such activity. In terms of distribution, the steady-state volume of distribution (VDss) values indicate moderate tissue distribution, and most compounds display low unbound fractions, reflecting strong binding to plasma proteins. Metabolic profiling shows that many compounds may interact with several CYP450 isoenzymes, particularly acting as inhibitors of CYP1A2, CYP2C19, and CYP2D6, which may influence metabolic rates and potentially lead to drug-drug interactions or prolonged half-life.

Excretion parameters show that most compounds possess low to moderate renal clearance values, suggesting that elimination through the kidneys occurs at a controlled rate. Total clearance values also remain within a moderate range, reducing the likelihood of accumulation in the body. Toxicity analysis indicates that most compounds do not exhibit hepatotoxicity or AMES mutagenicity, suggesting a generally favorable safety profile. However, several compounds, such as artocarpin and 3-prenyl luteolin, present lower maximum tolerated dose values, indicating potential toxicity at higher concentrations. Overall, the ADMET profiles of the *Artocarpus heterophyllus* compounds demonstrate good absorption, moderate distribution, potential metabolic interactions with key CYP450 enzymes, controlled excretion rates, and generally low toxicity risks, supporting their potential for further exploration as promising drug candidates.

CONCLUSION

This study demonstrates that phytochemical compounds derived from *Artocarpus heterophyllus* leaves exhibit promising interaction potential with the aromatase enzyme (PDB ID: 4GL7) based on comprehensive *in silico* molecular docking and pharmacokinetic evaluations. The docking validation process, supported by low RMSD values between crystallographic and redocked ligand poses, confirms the reliability of the applied docking protocol for predicting ligand-protein interactions. Several compounds, particularly 3-prenyl luteolin, prenyl caffeate, and artocarpanone, show favorable docking scores and stable binding orientations within the aromatase active site, indicating strong binding affinity comparable to, and in some cases exceeding, that of the reference inhibitor Letrozole. The observed interaction patterns, involving hydrogen bonding, aromatic interactions, and hydrophobic contacts with key active-site residues, suggest that these phytochemicals are capable of effectively occupying the catalytic pocket of aromatase. Drug-likeness analysis further reveals that all tested compounds generally comply with Lipinski's Rule of Five and Veber criteria, indicating suitable physicochemical properties for oral drug development. In addition, ADMET predictions suggest favorable absorption, moderate distribution, manageable metabolic profiles, and low toxicity risks for most compounds, although certain limitations, such as reduced intestinal absorption or potential CYP450 interactions in specific molecules, should be carefully considered. Overall, the findings of this study highlight *Artocarpus heterophyllus* as a valuable natural source of bioactive compounds with potential inhibitory activity against aromatase. While these *in silico* results provide important preliminary insights, further experimental validation through *in vitro* and *in vivo* studies is required to confirm the biological efficacy and safety of these compounds as prospective candidates for estrogen-dependent breast cancer therapy.

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