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Integrated In Silico Discovery of Bioactive Compounds from *Kaempferia galanga* L. Targeting Estrogen Receptor-β

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ABSTRACT

Introduction*: Estrogen receptor-β (ERβ) has emerged as a promising molecular target for the development of safer therapeutic agents for estrogen receptor-positive breast cancer due to its anti-proliferative and tumor-suppressive functions* ***Aims:*** *This study aimed to identify potential ERβ-targeting compounds from K. galanga through an integrated in silico approach combining molecular docking, protein–ligand interaction analysis, pharmacokinetic prediction, and toxicity evaluation.* ***Methods:*** *Eighteen phytochemical constituents of K. galanga were screened against the human ERβ ligand-binding domain (PDB ID: 1QKM) using AutoDock Vina. Docking protocol validation was performed by redocking the native ligand, while pharmacokinetic and toxicity profiles were predicted using ADMETlab 2.0.* ***Results:*** *Docking validation produced an RMSD value of 0.3460 Å, confirming the reliability of the docking protocol. Among the investigated compounds, 3-carene-5-one exhibited the strongest binding affinity (ΔG = −8.4 kcal/mol), followed by quercetin (ΔG = −8.0 kcal/mol) and kaempferol (ΔG = −7.1 kcal/mol). Quercetin displayed the most conserved interaction pattern with the key ERβ residues Glu305, Arg346, and His475, whereas 3-carene-5-one achieved superior affinity through extensive hydrophobic interactions. ADMET prediction indicated that 3-carene-5-one possessed more favorable membrane permeability and metabolic characteristics, while quercetin and kaempferol demonstrated comparatively safer nephrotoxicity, neurotoxicity, and hepatotoxicity profiles.* ***Conclusion****: The integrated in silico analysis identified 3-carene-5-one, quercetin, and kaempferol as the most promising ERβ-targeting candidates from K. galanga. Among them, 3-carene-5-one emerged as the most promising lead candidate owing to its superior binding affinity and balanced pharmacokinetic properties, while quercetin exhibited the most native ligand-like binding interactions, supporting further experimental validation for the development of novel ERβ-targeted phytopharmaceuticals.*

KEYWORDS: *Kaempferia galanga, estrogen receptor-β, molecular docking, ADMET.*

INTRODUCTION

The estrogen receptor-β (ERβ) is a nuclear hormone receptor subtype that, together with estrogen receptor-α (ERα), mediates the physiological effects of estrogen throughout the body. Unlike ERα, which predominantly drives cell proliferation and is closely linked to

hormone-dependent breast cancer, ERβ is generally regarded as an anti-proliferative, tumour suppressor receptor that also mediates bone-protective, neuroprotective, and cardioprotective estrogenic effects (Božović et al., 2021). Because of the favourable pharmacological profile, ERβ-selective agonism, rather than non-selective activation of both receptor subtypes, is considered a safer therapeutic strategy for conditions such as menopausal symptoms, osteoporosis, and certain hormone-responsive cancers, and has motivated extensive searches for selective natural or synthetic ERβ ligands (Fleischer et al., 2021; Ortona et al., 2022)

The pharmacological properties of *Kaempferia galanga* L. are closely associated with its rich phytochemical composition. Previous studies have identified numerous secondary metabolites, including phenylpropanoids, flavonoids, monoterpenoids, and coumarins, which collectively contribute to its antioxidant, anti-inflammatory, antimicrobial, and anticancer activities (Wang et al., 2021)suggesting their potential to interact with Estrogen Receptor-β (ERβ)

Kaempferia galanga L. locally known in Indonesia as *kencur*, is a small rhizomatous herb of the *Zingiberaceae* family that has long been used in traditional medicine as an analgesic, anti-inflammatory, antitussive, and general tonic remedy, and more recently as a raw material in the herbal and nutraceutical industries (Wang et al., 2021).Among these compounds, kaempferol has been reported to promote osteoblastic differentiation through an estrogen-receptor-dependent mechanism (Xiong et al., 2021). Several in silico studies have explored the interactions between *K. galanga* metabolites and PD-L1 in the context of cancer immunotherapy (Eka Putra et al., 2025).

Currently, limited studies report has systematically investigated the major phytochemicals of *K. galanga* rhizome against the ERβ ligand-binding domain and integrated the docking results with a comprehensive, detailed protein ligand interaction analysis an integrated ADMET/toxicity evaluation. Therefore, this study aimed to identify compounds exhibiting favourable binding affinity together with desirable pharmacokinetic and toxicity profiles.bioactive compounds from *Kaempferia galanga* L. against the Estrogen Receptor-β.

METHODS

The hardware used in this studi was a unit of computer with Windows 10 Pro 64-bit operating system, Intel® Core™ i5-4210U, 4 GB of RAM, and 2 GB NVIDIA Geforce.

Ligand Preparation

The test compounds used for molecular docking were selected based on phytochemical constituents previously reported in the rhizome of *Kaempferia galanga* L. (Adianingsih et al., 2021; Fadhiel Ihsan et al., n.d.; Muzzazinah et al., 2024; Supandi et al., 2021; Zeng et al., n.d.). The Three-dimensional (3D) structures of ligands were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). The three-dimensional structures were prepared and energy-optimized using AutoDock Tools 1.5.7 by defining the appropriate rotatable bonds prior to molecular docking. Genistein, the co-crystallized ligand of ERβ, was used as the native ligand.

Receptor Preparation

The estrogen receptor-β (ERβ) was downloaded from the RCSB Protein Data Bank (RCSB PDB), under the PDB ID 1QKM. The receptor was prepared by removing water molecules and other heteroatoms. The co-crystallized ligand (genistein) was extracted from the receptor and used for docking validation. Kollman united-atom charges were subsequently added to the receptor structure prior to docking. The prepared receptor was then saved in PDBQT format for molecular docking simulations (Morris et al., 2009).

Docking Molecular

Molecular docking simulations were performed using AutoDock Vina, while AutoDock Tools 1.5.7 was used for receptor and ligand preparation. The docking grid box was centered on the binding pocket occupied by the co-crystallized ligand (genistein), encompassing the binding residues. Docking validity was confirmed through redocking analysis, where an RMSD value below 2.0 Å was considered acceptable. The docked complexes were subsequently visualized using BIOVIA Discovery Studio Visualizer 2021, and protein–ligand interactions, including hydrogen bonds, hydrophobic interactions, and interacting amino acid residues, were analyzed.

Pharmacokinetics Profile and Toxicity

The pharmacokinetic and toxicity properties of all selected compounds were predicted using the ADMETlab 2.0 web server (https://admetmesh.scbdd.com). The prediction was performed by uploading the Simplified Molecular Input Line Entry System (SMILES) strings of the bioactive compounds from Kaempferia galanga L. into the platform

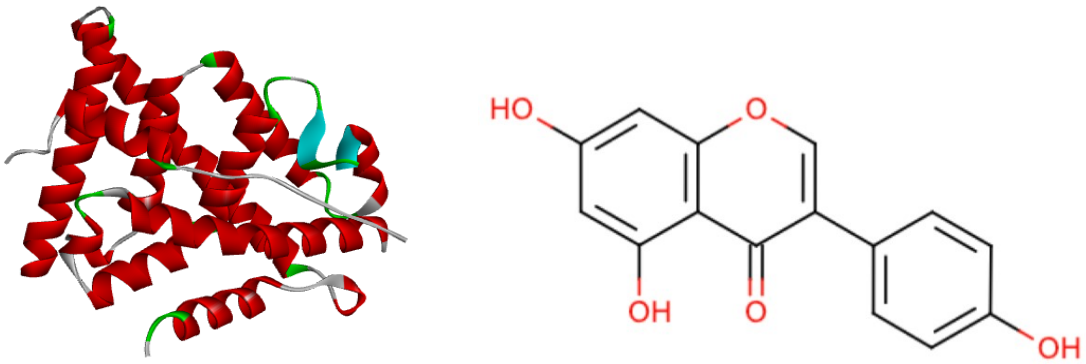
RESULTS AND DISCUSSION

Ligand Selection

Ligand selection was performed according to four predefined criteria, that the compound had been identified as a major secondary metabolite or bioactive constituent of *K. galanga* rhizomes in phytochemical studies (Table 1); the compound had previously demonstrated relevant pharmacological

Table 1. Bioactive compound from *Kaempferia galanga* L

No	Bioactive Compounds	No	Bioactive Compounds
1	Ethyl p-methoxycinnamate (EPMC)	10	1,8-Cineole (Eucalyptol)
2	Ethyl cinnamate	11	p-Cymene
3	p-Methoxycinnamic acid	12	p-Cymene-8-ol
4	Cinnamic acid	13	Eucarvone
5	3-Carene-5-one	14	Carvone
6	Camphene	15	Kaempferol
7	Camphor	16	Kaempferide
8	Isoborneol	17	Quercetin
9	Borneol	18	Coumarin



A B

Figure 1. The estrogen receptor-β (ERβ) (A) and Native Ligan (Genistein) (B)

activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, or estrogen receptor-related biological activities; and its chemical structure was publicly available in the PubChem database, allowing retrieval of a three-dimensional (3D) structure for molecular docking.

Docking Molecular

Validation of Docking Method

The first step of the molecular docking study was the validation of the docking protocol to ensure the reliability of the docking procedure. Validation was performed by re-docking the co-crystallized ligand (genistein) into the ligand-binding domain of Human Estrogen Receptor-β (ERβ; PDB ID: 1QKM). The docking simulations were carried out using a grid box centered on the native ligand-binding site with coordinates of X = 22.438, Y = 8.003, and Z = 111.538 Å, and dimensions of 40 × 40 × 40 Å, thereby encompassing the entire ligand-binding pocket and the key amino acid residues involved in ligand recognition.

The validity of the docking protocol was evaluated based on the root mean square deviation (RMSD) between the experimentally determined ligand pose and the predicted docking pose. An RMSD value of less than 2.0 Å is generally considered indicative of a reliable docking protocol capable of accurately reproducing the crystallographic binding conformation (Osman et al., 2020). In the

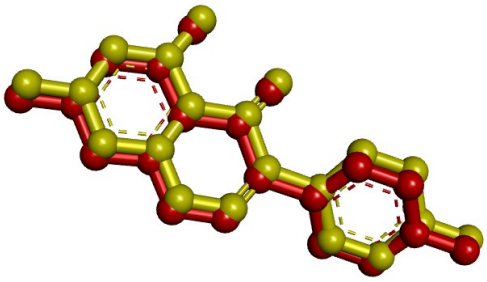


Figure 2. Overlay of the redocked ligand (yellow) and the co-crystallized native ligand (red).

present study, the re-docking procedure produced an RMSD value of 0.3460 Å, indicating excellent agreement between the predicted and experimental ligand conformations. The superimposition of the redocked ligand and the co-crystallized ligand further demonstrated a high degree of structural overlap (Figure 1), confirming that the selected docking parameters were appropriate for subsequent molecular docking of the Kaempferia galanga L. bioactive compounds against the ERβ ligand-binding domain. Validation was performed through a redocking process, where the ligand was repositioned into the same active site of the receptor from its original location in the crystalstructure (Figure 2).

The docking results were assessed based on the predicted binding free energy (ΔG), which represents the thermodynamic stability of the receptor–ligand complex. In molecular docking studies, lower (more negative) ΔG values indicate stronger binding affinity and greater stability of the ligand within the receptor binding pocket, suggesting a higher probability of biological activity (Pantsar & Integrated In Silico of *Kaempferia galanga* L. Poso, 2018). The docking results (Table 2) demonstrated considerable variation in binding affinity among the investigated phytochemicals, with ΔG values ranging from −4.3 to −8.4 kcal/mol. The native ligan, exhibited a binding free energy of −8.0 kcal/mol, which served as the reference for evaluating the docking performance of the tested compounds. Interestingly, 3-carene-5-one showed the lowest binding free energy (−8.4 kcal/mol), indicating a stronger predicted interaction with ERβ than the native ligand. This result suggests that 3-carene-5-one possesses a molecular conformation that fits favorably within the hydrophobic ligand-binding cavity of ERβ, thereby promoting stable receptor–ligand complex formation.

Among the bioactive compounds, quercetin exhibited a binding affinity identical to that of native ligan (−8.0 kcal/mol), whereas kaempferol displayed a relatively high binding affinity (−7.1 kcal/mol). These findings are particularly noteworthy because flavonoids are well recognized as naturally occurring phytoestrogens capable of interacting with estrogen receptors through structural similarities to endogenous estrogens. The comparable docking score obtained for quercetin suggests that this compound may occupy the ERβ ligand-binding pocket in a manner similar to the native ligand. Previous studies have demonstrated that flavonoids possessing multiple hydroxyl groups generally exhibit stronger receptor binding due to their ability to establish multiple hydrogen bonds

Table 2. Binding free energy and binding interaction

Ligand	ΔG (kcal/mol)	Binding Interaction
Native ligand	-8.0	H-bond: Glu305, Arg346, His475; Pi-Sigma: Met336; Pi-alkyl: Leu339, Leu343, Ala302, Leu476, Leu298; Pi-pi T-shaped: Phe356
Ethyl p-methoxycinnamate (EPMC)	-6.2	Carbon H-bond: Gly472; Alkyl/Pi-alkyl: Ala302, Leu339, Leu298, His475, Met295, Leu476
Ethyl cinnamate	-6.9	Pi-Sigma: Met336; Alkyl/Pi-alkyl: Ala302, Leu339, Leu298, Leu476, Phe356, Leu343
p-Methoxycinnamic acid	-4.8	Carbon H-bond: Leu339, Glu305; Pi-pi T-shaped: Phe356; Alkyl/Pi-alkyl: Leu343, Ala302, Leu476, Met295
Cinnamic acid	-6.3	Carbon H-bond: Thr299; Pi-pi T-shaped: Phe356; Pi-alkyl: Ala302, Leu339, Leu343
3-Carene-5-one	-8.4	Pi-Sulfur: Met336; Pi-pi T-shaped: Phe356; Alkyl/Pi-alkyl: Leu339, Leu343, Met295, Leu476, His475, Ile373, Leu298, Ile376, Phe377
Camphene	-5.5	Alkyl/Pi-alkyl: Met336, Leu298, Leu339, Ala302, Leu343, Phe356
Camphor	-4.5	Alkyl/Pi-alkyl: Ala302, Leu339, Leu298, Met336, Phe356, Leu301
Isoborneol	-4.3	Conventional H-bond: Leu339; Alkyl/Pi-alkyl: Met340, Leu301, Trp335, Met336, Leu298, Ala302, Phe356
Borneol	-4.3	Alkyl/Pi-alkyl: Trp335, Leu339, Leu301, Met340, Met336, Leu298, Ala302, Phe356
1,8-Cineole (Eucalyptol)	-4.7	Alkyl/Pi-alkyl: Leu298, Phe356, Ile376, Met340, Ile373, Met336, Leu476
p-Cymene	-6.4	Pi-Sulfur: Met336; Alkyl/Pi-alkyl: Ala302, Met295, Leu476, Phe356, Leu298
p-Cymene-8-ol	-6.1	Pi-Sulfur: Met340, Met336; Pi-pi T-shaped: Phe356; Alkyl/Pi-alkyl: Leu298, Ala302, Met295, Ile376, Ile373, Leu339
Eucarvone	-6.5	Alkyl/Pi-alkyl: Phe356, Leu476, Ala302, Val487, Met336, Ile373, Leu298, Ile376, Phe377, Met340
Carvone	-6.5	Alkyl/Pi-alkyl: Ile376, Phe377, Ile373, Leu298, Phe356, Leu380, Leu301, Leu339, Ala302
Kaempferol	-7.1	Conventional H-bond: His475; Carbon H-bond: Met340; Pi-Sigma: Met336; Pi-pi T-shaped: Phe356; Pi-alkyl: Leu476, Leu339, Ala302, Leu298, Leu343
Kaempferide	-4.3	Conventional H-bond: His475; Pi-Sigma: Met336, Met295; Alkyl/Pi-alkyl: Leu298, Leu339, Ala302, Met340, Val484, Leu476, Met479
Quercetin	-8.0	Conventional H-bond: Arg346, Glu305, Leu298, Leu339; Pi-Sigma: Met336; Pi-pi T-shaped: Phe356; Pi-alkyl: Met340, Leu343, Leu476
Coumarin	-6.6	Conventional H-bond: His475; Pi-Sigma: Met336, Leu298, Leu339, Ala302, Leu343, Phe356; Pi-alkyl: Leu476, Ala302

while simultaneously maintaining hydrophobic interactions within the receptor cavity (Božović et al., 2021; Xiong et al., 2021).

Ethyl cinnamate showed the strongest affinity within this group (−6.9 kcal/mol), followed by coumarin (−6.6 kcal/mol), eucarvone (−6.5 kcal/mol), carvone (−6.5 kcal/mol), p-cymene (−6.4 kcal/mol), cinnamic acid (−6.3 kcal/mol), ethyl p-methoxycinnamate (EPMC) (−6.2 kcal/mol), and p-cymene-8-ol (−6.1 kcal/mol). Although these compounds exhibited lower binding affinities than quercetin or 3-carene-5-one, their ΔG values indicate favorable interactions with the receptor, suggesting that the aromatic phenylpropanoid scaffold contributes positively to receptor recognition through

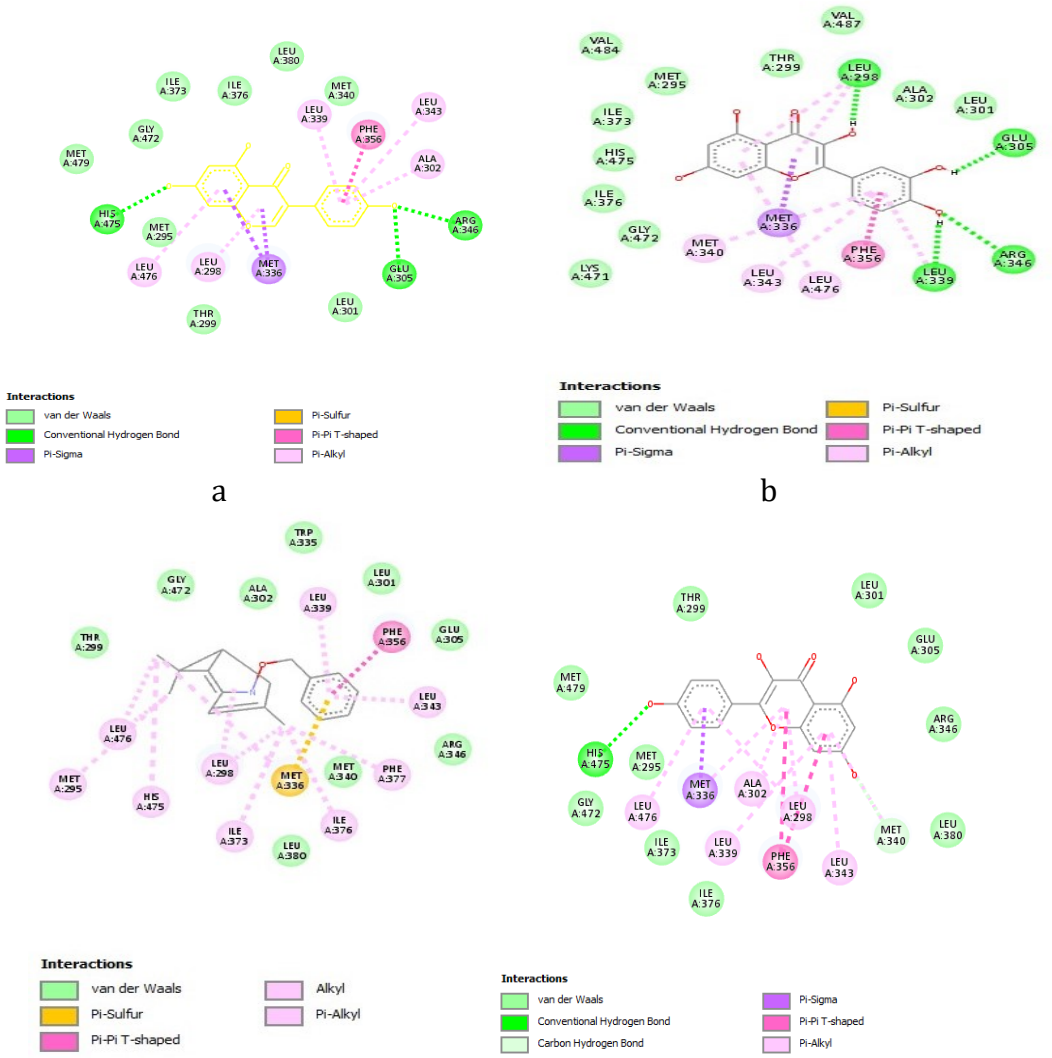


Figure 3. Receptor-ligand interaction: native ligand (a), quercetin (b), 3-carene-5-one (c), and kaempferol (d)

hydrophobic and π-related interactions. In contrast, camphor (−4.5 kcal/mol), borneol (−4.3 kcal/mol), isoborneol (−4.3 kcal/mol), kaempferide (−4.3 kcal/mol), and 1,8-cineole (−4.7 kcal/mol), displayed relatively weak binding affinities. These compounds generally possess smaller molecular frameworks and fewer functional groups capable of forming stabilizing hydrogen bonds with amino acid residues located in the ERβ ligand-binding domain.

Among all investigated compounds, 3-carene-5-one, quercetin, and kaempferol emerged as the most promising candidates based on their favorable binding free energies. Among all investigated compounds, 3-carene-5-one, quercetin, and kaempferol emerged as the most promising candidates based on their favorable binding free energies.

Reseptor-Ligand Interaction

Therefore, protein–ligand interaction analysis was performed to evaluate the molecular basis underlying the binding affinity

of each phytochemical. The interaction profiles of the docked ligands are summarized in Table 2.

The native ligand established three conventional hydrogen bonds with the highly conserved residues Glu305, Arg346, and His475, accompanied by π-sigma interaction with Met336, π–π T-shaped interaction with Phe356, and several π-alkyl interactions involving Leu298, Ala302, Leu339, Leu343, and Leu476. In particular, the hydrogen-bonding network involving Glu305–Arg346–His475 has been recognized as a characteristic feature of ERβ agonist binding and is essential for receptor activation. (See figure 3.A) Among the investigated compounds, quercetin demonstrated the interaction profile most closely resembling that of the native ligand (See Figure 3.B). Quercetin formed conventional hydrogen bonds with Arg346 and Glu305, in addition to interactions with Leu298 and Leu339, while maintaining π-sigma interaction with Met336, π–π T-shaped interaction with Phe356, and π-alkyl interactions with Met340, Leu343, and Leu476. The preservation of hydrogen bonds with Arg346 and Glu305, together with extensive hydrophobic interactions, likely explains its binding affinity (−8.0 kcal/mol), which was identical to that of native ligan. Interestingly, 3-carene-5-one, despite exhibiting the lowest binding free energy (−8.4 kcal/mol), did not form conventional hydrogen bonds with the conserved catalytic residues. Instead, this monoterpenoid established π-sulfur interaction with Met336, π–π T-shaped interaction with Phe356, and extensive hydrophobic contacts involving Leu298, Leu339, Leu343, Met295, Leu476, His475, Ile373, Ile376, and Phe377 (See Figure 3.C). The large number of hydrophobic interactions appears to compensate for the absence of hydrogen bonding, resulting in a highly stable receptor–ligand complex.

Kaempferol formed a conventional hydrogen bond with His475, a carbon hydrogen bond with Met340, π-sigma interaction with Met336, π–π T-shaped interaction with Phe356, and several π-alkyl interactions involving Leu298, Ala302, Leu339, Leu343, and Leu476. Although kaempferol interacted with only one of the three conserved hydrogen-bonding residues, the combination of hydrogen bonding and hydrophobic contacts contributed to its relatively high binding affinity (−7.1 kcal/mol) (See Fig.3D).

Pharmacokinetic Profile and Toxicity

To complement the molecular docking results, the three compounds exhibiting the most favorable binding affinities toward Human Estrogen Receptor-β (ERβ), namely 3-carene-5-one, kaempferol, and quercetin, were further evaluated using ADMETlab 2.0 to predict their pharmacokinetic behavior. The assessment included absorption, distribution, metabolism, and excretion (ADME) parameters to identify compounds possessing strong receptor binding.

Table 3. ADME prediction

Compounds	Absorbtion			Distribution				Metabolism								Ekscretion	
	Caco-2	HIA	MDCK	VDss	PPB (%)	Fu	BBB	CYP1A2 substrate	CYP1A2 inhibitor	CYP3A4 Substrat	CYP3A4 Inhibitor	CYP2D6 substrate	CYP2D6 inhibitor	CYP2C9 substrate	CYP2C9 inhibitor	CL Plasma	T1/2
3-Carene-5-one	-4.7	---	0	1.36	97.6	2.4	-	--	--	---	+++	-	--	-	-	8.88	0.68
Kaempferol	-5.9	---	0	0.15	97.9	1.4	---	+	+++	---	+++	+++	---	+	+	5.69	1.38
Quercetin	-6.1	--	0	0.13	98.7	1.1	---	-	+++	---	+++	+++	---	---	+ -	8.28	1.58

The predicted intestinal permeability, represented by the Caco-2 parameter, showed noticeable differences among the three compounds (Table 3). 3-Carene-5-one exhibited a Caco-2 value of −4.7, indicating higher predicted membrane permeability than kaempferol (−5.9) and quercetin (−6.1). In general, compounds with less negative Caco-2 values are expected to diffuse more readily across intestinal epithelial cells, resulting in improved oral absorption (Xiong et al., 2021).

Distribution analysis revealed that all three compounds possessed high plasma protein binding (PPB), ranging from 97.6% to 98.7%, indicating that only a small proportion of the compounds would remain unbound in plasma. Quercetin showed the highest PPB (98.7%) and the lowest fraction unbound (Fu = 1.1%), followed by kaempferol (97.9%; Fu = 1.4%) and 3-carene-5-one (97.6%; Fu = 2.4%).

Cytochrome P450 prediction demonstrated substantial differences in metabolic behavior between monoterpenoids and flavonoids. 3-Carene-5-one showed minimal interaction with most CYP isoenzymes, being predicted as a substrate only for CYP2D6, while showing no inhibitory activity toward CYP1A2, CYP3A4, CYP2D6, or CYP2C9. Such a profile suggests a relatively low risk of metabolic drug–drug interactions.

In contrast, kaempferol and quercetin demonstrated more complex metabolic profiles. Both compounds were predicted to interact with multiple CYP isoforms, particularly CYP3A4 and CYP2D6, indicating potential susceptibility to metabolic interactions. Moreover, kaempferol exhibited inhibitory activity toward CYP1A2 and CYP2C9, whereas quercetin was predicted to inhibit CYP2D6. Consequently, despite their favorable receptor binding, the metabolic profiles of kaempferol and quercetin may require careful consideration during subsequent drug development.

The predicted plasma clearance (CL) values indicated moderate elimination rates for all three compounds. 3-Carene-5-one showed a clearance value of 8.884

Table 4. Toxicity prediction

Compounds	Toxicity							Toxicophore				
	AMES Toxicity	hERG Blockers	Drug-induced Nephrotoxicity	Drug-induced Neurotoxicity	Human Hepatotoxicity	Carcinogencity	FDAMDD	Genotoxic Carcinogenicity Rule	Non Genotoxic Carcinogenicity Rule	Aquatic Toxicity Rule	Skin Sensitization Rule	Acute Toxicity Rule
3-Carene-5-one	0.59	0.15	0.22	0.74	0.52	0.60	0.43	0	0	0	0	0
Kaempferol	0.54	0.06	0.01	0.03	0.38	0.71	0.80	0	0	0	4	0
Quercetin	0.58	0.05	0.01	0.00	0.33	0.6	0.79	0	0	0	8	0

mL/min/kg, slightly higher than quercetin (8.28 mL/min/kg) and substantially higher than kaempferol (5.69 mL/min/kg). Meanwhile, the predicted half-life (T1/2) varied from 0.68 h for 3-carene-5-one to 1.586 h for quercetin. The shorter half-life of 3-carene-5-one may result in faster elimination, whereas the longer half-life of quercetin may prolong systemic exposure despite its lower permeability. Overall, all compounds demonstrated a relatively low probability of cardiotoxicity (Table 4), as indicated by low hERG blocker scores ranging from 0.05 to 0.15, suggesting a minimal risk of QT interval prolongation and cardiac arrhythmia (Vandenberg et al., 2012). Regarding nephrotoxicity, kaempferol and quercetin exhibited very low predicted probabilities (0.01), whereas 3-carene-5-one showed a slightly higher value (0.22), although still within an acceptable range for preliminary screening. A more pronounced difference was observed in neurotoxicity prediction, where quercetin (0.00) and kaempferol (0.03) demonstrated markedly lower probabilities than 3-carene-5-one (0.74), indicating a potentially superior neurological safety profile of the flavonoids. Similarly, the predicted probability of human hepatotoxicity was lowest for quercetin (0.33), followed by kaempferol (0.38), whereas 3-carene-5-one showed a higher value (0.52). Furthermore, none of the investigated compounds triggered the genotoxic carcinogenicity, non-genotoxic carcinogenicity, aquatic toxicity, or acute toxicity toxicophore rules, indicating the absence of structural alerts associated with severe toxicological liabilities. However, kaempferol and quercetin exhibited four and eight predicted skin sensitization alerts, respectively, whereas 3-carene-5-one showed no structural alert for skin

sensitization, suggesting a lower probability of inducing allergic skin reactions. When integrated with the molecular docking and pharmacokinetic analyses, these findings indicate that 3-carene-5-one remains the most promising lead compound because it combines the strongest binding affinity toward Estrogen Receptor-β (ΔG = −8.4 kcal/mol), a favorable pharmacokinetic profile, and an acceptable overall toxicity profile despite requiring further investigation regarding its predicted neurotoxicity and hepatotoxicity. Conversely, quercetin and kaempferol exhibited comparatively safer systemic toxicity profiles but less favorable pharmacokinetic characteristics, highlighting the importance of integrating receptor affinity, ADMET, and toxicity prediction to prioritize lead compounds before experimental validation (Xiong et al., 2021).

CONCLUSION

Through an integrated computational approach, 3-carene-5-one, quercetin, and kaempferol from K. galanga were identified as promising ERβ ligands. While 3-carene-5-one achieved the highest binding affinity and better ADMET properties, quercetin and kaempferol offered superior safety profiles and key receptor interactions. Conclusively, 3-carene-5-one stands out as the primary lead compound, supported by the two flavonoids as complementary Integrated In Silico of *Kaempferia galanga* L. candidates. This study justifies further experimental research to evaluate these compounds as novel therapeutics for ER-positive breast cancer.

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