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Potential of Active Compounds in Broadleaf Mahogany (*Swietenia macrophylla*) Seeds Against Breast Cancer Cells Based on *In Silico* Study

Potensi Senyawa Aktif Biji Mahoni Berdaun Lebar (*Swietenia macrophylla*) terhadap Sel Kanker Payudara Berdasarkan Studi *In Silico*

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ABSTRACT

Breast cancer is a leading cause of cancer-related deaths in Indonesia. However, the drugs that are commonly used for treatment can cause side effects and become resistant over time. A study was conducted to test the cytotoxic activity of broadleaf mahogany (*Swietenia macrophylla*) seed extract on MCF-7 breast cancer cells in vitro. The study aimed to predict active compounds in the broadleaf mahogany seeds that have the potential to act as anti-breast cancer agents using in silico analysis. Molecular docking, visualization of the interaction between the receptor and the ligands, and physicochemical analysis were used to determine the most promising compounds. The receptors used were fibroblast growth factor receptor 1 (FGFR1), vascular endothelial growth factor receptor 2 (VEGFR2), insulin-like growth factor type 1 receptor (IGF-1R), estrogen receptor (ER-α), and progesterone receptor (PR). The results showed that 12 compounds have the potential to be active as anti-breast cancer agents. Three of these compounds, 3β,6-dihydroxydihydrocarapine, stigmasterol, and 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one, were predicted to have similar mechanisms of inhibition as a comparator drug based on binding site similarity values. These compounds are predicted to be taken orally and are promising for further research.

Keywords: MCF-7, stigmasterol, molecular docking, limonoid, oral drug

ABSTRAK

Kanker payudara merupakan penyebab utama kematian akibat kanker di Indonesia. Namun, obat-obatan yang biasa digunakan dilaporkan dapat menimbulkan efek samping dan menjadi resisten seiring berjalannya waktu. Penelitian menentukan aktivitas sitotoksik ekstrak biji mahoni berdaun lebar (*Swietenia macrophylla*) terhadap sel kanker payudara MCF-7 secara *in silico* perlu dilakukan. Penelitian ini bertujuan untuk memprediksi senyawa aktif pada biji mahoni berdaun lebar yang berpotensi sebagai agen anti kanker payudara dengan menggunakan analisis in silico. Penambatan molekul, visualisasi interaksi antara reseptor dan ligan, dan analisis fisikokimia digunakan untuk menentukan senyawa yang paling menjanjikan. Reseptor yang digunakan adalah reseptor faktor pertumbuhan fibroblas 1 (FGFR1), reseptor faktor pertumbuhan endotel vaskular 2 (VEGFR2), reseptor faktor pertumbuhan mirip insulin tipe 1 (IGF-1R), reseptor estrogen (ER-α), dan reseptor progesteron (PR). Hasil penelitian menunjukkan 12 senyawa berpotensi aktif sebagai agen anti kanker payudara. Tiga dari senyawa tersebut, 3β,6-dihydroxydihydrocarapine, stigmasterol, dan 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-

one, diperkirakan memiliki mekanisme penghambatan yang serupa dengan obat pembanding berdasarkan nilai kesamaan situs yang mengikat. Senyawa ini diperkirakan dapat dikonsumsi secara oral dan menjanjikan untuk penelitian lebih lanjut.

Kata Kunci: MCF-7, stigmasterol, penambatan molekul, limonoid, obat oral

INTRODUCTION

Research on breast cancer continues to advance, with a primary focus on mitigating both the direct detrimental effects of breast cancer cells and the adverse impacts of chemotherapy. Typically, the pathways targeted for developing anti-breast cancer drugs involve hormone regulation and receptor tyrosine kinases (RTK) (Zhao & Ramaswamy, 2014). The estrogen receptor (ER) is pivotal in regulating crucial gene expressions related to proliferation and survival in both normal and cancerous cells (Zhao & Ramaswamy, 2014). Additionally, ER can activate the progesterone receptor (PR), leading to alterations in the estrogen receptor alpha (ERα) binding site on DNA, consequently affecting ERα function (Choucair, 2018). Notably, ERα is expressed in approximately 75% of breast cancer cases, with half of these cases also expressing PR (Zattarin et al., 2020). Moreover, ER can undergo ligand-independent activation due to downstream signaling from RTK (Zhao & Ramaswamy, 2014).

RTKs implicated in breast cancer growth include fibroblast growth factor receptor 1 (FGFR1), vascular endothelial growth factor receptor 2 (VEGFR2), and insulin-like growth factor type 1 receptor (IGF-1R). FGFR1 amplification is observed in various cancers such as non-small cell lung carcinoma, head and neck tumors, ovarian cancer, and breast cancer (Erber et al., 2020). VEGFR2 has been identified in breast, lung, ovarian, and renal cell carcinomas, with its presence particularly noted in the most aggressive form of breast cancer, triple-negative breast cancer (TNBC) (Lian et al., 2019). IGF-1R serves as a crucial target for tumorigenesis and growth, with its ligand, insulin-like growth factor type 1 (IGF-1), acting as a potent mitogen in several cancer types (Chen & Sharon, 2013). Tamoxifen currently serves as a primary breast cancer drug by blocking estrogen receptors, yet its usage is associated with resistance and adverse effects including blood clots, stroke, uterine cancer, and cataracts (Mathew & Raj, 2009). Given these drawbacks, there is a pressing need to explore safer drug candidates derived from natural sources.

One such potential source is broadleaf mahogany (Swietenia macrophylla), abundantly found in Indonesia. Its seeds contain a plethora of compounds including limonoids, fatty acids, and steroids (Telrandhe et al., 2022). Traditionally, mahogany seeds have been utilized in treating conditions such as high blood pressure, diabetes, and infections. Studies have demonstrated the anti-inflammatory properties of S. macrophylla seeds attributed to swietenine compounds. Furthermore, the leaf extract of S. macrophylla, rich in limonoid compounds, exhibits significant cytotoxicity against colorectal cancer cells with an IC50 value of 55.87 μg/ml (Pinto et al., 2021). Additionally, limonoid compounds isolated from S. macrophylla extract have shown promising anticancer activity against various cancer cell lines, including A375 cells with an IC50 value of 9.8 μM (Wang et al., 2022). The most active fraction of the ethyl acetate extract of S. macrophylla seeds showed positive results on the triterpenoid test and had cytotoxic activity against MCF-7 breast cancer cells with an IC50 of 34.11 μg/mL (Tohir et al., 2020). However, the potential anti-breast cancer properties of compounds derived from S. macrophylla seeds remain largely unexplored.

Molecular docking presents a valuable approach to elucidate the active compounds within S. macrophylla seeds with potential anti-breast cancer properties. Molecular docking involves computational simulations to predict ligand orientation and binding stability with a target, providing insights into the ligand-receptor complex's binding affinity (ΔG binding) (Nogara et al., 2015). Autodock Vina is a widely used software for molecular docking due to its accessibility, speed, and accuracy (Yasman et al., 2020). This study aims to predict active compounds in S. macrophylla seeds with potential anti-breast cancer activity through molecular docking analysis, shedding light on promising candidates for further investigation.

METHODS

1. Ligands and Receptors Preparation

The ligand preparation process involved obtaining a total of 80 compounds from *S. macrophylla* seeds (referred to as test ligands) along

with four comparator ligands (tamoxifen, onapristone, NVP-AEW541, and lucitanib) from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in *sdf format. Subsequently, the file format was converted to *pdb using MarvinView. The test ligands underwent optimization by the addition of hydrogen atoms using AutoDock Tools version 1.5.6 and were saved in *pdbqt format for further analysis. The receptors used were FGFR1 (3C4F), VEGFR2 (2P2I), IGF-1R (2OJ9), ER-α (1SJ0), PR (3KBA) obtained from the Protein Data Bank (PDB) website (www.rscb.org/pdb) in *pdb format. These receptors were meticulously prepared by separating natural ligands and eliminating water molecules and attached residues using the Discovery Studio software Visualizer. Subsequently, the prepared receptors underwent optimization through AutoDock Tools version 1.5.6, wherein hydrogen atoms were added, and the optimized results were saved in *pdbqt format for subsequent analysis.

2. Molecular Docking Validation

During the receptor preparation process, the natural ligands were separated, and subsequently, re-docking experiments were conducted with their respective receptors using AutoDock Tools version 1.5.6. Molecular docking validation was performed using four grid box sizes spaced 0.375 Å apart, centered on the coordinates of the corresponding natural ligands. This process was iterated ten times. The grid box size that yielded the lowest Root Mean Square Deviation (RMSD) value was selected for the subsequent molecular docking analyses.

3. Molecular Docking Simulation

Molecular docking experiments were conducted on both the test and control ligands against the respective receptors using AutoDock Vina version 1.5.6. Docking calculations were performed with grid box size, spacing, and coordinate points determined based on the validation results. A configuration file named "conf.txt" was generated within the Vina folder, containing information regarding the size and coordinates of the grid box. Subsequently, the program was executed via the CMD (Command Prompt) window using the command "C:\vina.exe --config conf.txt --log log.txt". The results obtained were in the form of *pdbqt files along with a document named "log.txt" containing the ΔG values. The ΔG values obtained from the test ligands were compared with those from the control ligands to assess the spontaneity of the interactions within the ligand-receptor complexes. A test ligand exhibiting a more negative ΔG value compared to the reference ligand was identified as the selected test ligand 1.

4. Molecular Docking Visualization

Molecular docking visualization was conducted specifically on the selected ligand 1 to elucidate the interactions formed between the ligand and the receptor. The comparison of the binding site similarity between selected ligand 1 and the control ligand was quantified using the Binding Site Similarity value (%BSS), aiming to discern the inhibition mechanism. The selected ligand model 1 was integrated with the receptor using Discovery Studio Visualizer and saved in *pdb format. Subsequently, the %BSS was calculated using equation (1). Ligands exhibiting a %BSS exceeding 50% were categorized as selected ligands 2.

$$\%BSS = \frac{\text{The number of amino acid residues that interact with the test ligand}}{\text{The number of amino acid residues that interact with the control ligand}} \times 100\% \ldots (1)$$

5. Physicochemical Analysis

Selected ligands 2 were analyzed for their physicochemical properties using the website http://swissadme.ch/. The compound structures were uploaded in *sdf format and converted to SMILES code. The analysis was conducted based on parameters aligned with the Lipinski rule, which includes criteria such as molecular weight less than 500 g/mol, hydrogen bond donors fewer than five, hydrogen bond acceptors fewer than ten, and logP less than five.

RESULTS & DISCUSSION

1. Anticancer Active Compounds in *Swietenia macrophylla*

Breast cancer stands as a leading cause of cancer-related mortality in Indonesia, underscoring the urgent need for advancements in drug development and therapies to combat this disease. Key receptors closely associated with cancer activity include progesterone receptor (PR), estrogen receptor alpha (ERα), insulin-like growth factor 1 receptor (IGF-1R), fibroblast growth factor receptor 1 (FGFR-1), and vascular endothelial growth factor receptor 2 (VEGFR-2). Blocking the activity of these receptors holds promise for the development of anti-breast cancer drugs. PR expression is typically observed in

early-stage breast cancer without metastasis (Comşa et al., 2015). Both PR and ERα play sequential roles in pubertal breast development primarily through paracrine mechanisms (Trabert et al., 2020). Conversely, IGF-1R activity fosters cancer cell proliferation, migration, and invasion, contributing to tumor metastasis, treatment resistance, and poor patient prognosis (Sun et al., 2017). Activation of FGFR1 and VEGFR2 exacerbates breast cancer aggressiveness and metastasis. In the analysis of test ligand activity against the progesterone receptor, onapristone serves as a comparative ligand. Onapristone, an antiprogestin, directly interacts with the hormone-binding site of PR, competitively inhibiting progesterone binding to the receptor (Vegeto et al., 1996). Lucitanib, a potential drug candidate undergoing clinical trials, selectively inhibits FGFR1 and VEGFR2 in metastatic breast cancer patients. Functioning as a tyrosine kinase inhibitor (TKI), lucitanib targets allosteric sites on receptors, thereby reducing tyrosine kinase phosphorylation and inhibiting cell proliferation (Jiao et al., 2018). The process of drug development often commences with prediction and simulation stages focusing on the interaction of candidate compounds with receptors. Molecular docking emerges as a suitable method for this purpose, facilitating the identification of promising compounds for further investigation and potential therapeutic use.

In molecular docking, precise alignment of the target receptors with the test and control ligands is essential for accurate analysis. The receptors utilized in this study included estrogen receptor alpha (ERα, PDB ID: 1SJ0), progesterone receptor (PR, PDB ID: 3KBA), insulin-like growth factor 1 receptor (IGF-1R, PDB ID: 2OJ9), vascular endothelial growth factor receptor 2 (VEGFR2, PDB ID: 2P2I), and fibroblast growth factor receptor 1 (FGFR1, PDB ID: 3C4F). Control ligands employed comprised tamoxifen, onapristone, NVP-AEW541, and lucitanib. The test ligands encompassed 80 compounds extracted from Swietenia macrophylla seeds, belonging to various classes such as limonoids, steroids, terpenoids, alkaloids, flavonoids, coumarins, and saponins. Rigorous preparation of ligands and receptors aimed to optimize their structures, ensuring the accuracy of molecular docking outcomes. Ligands and receptors underwent a validation stage to verify their suitability for molecular docking. Notably, all receptors demonstrated root mean square deviation (RMSD) values <2 Å, indicating their suitability for molecular docking (Table 1). It's noteworthy that the natural ligand for IGF-1R exhibited the highest RMSD value, primarily due to an aberration in the position of the imidazole group. This deviation led to a perpendicular orientation between the redocked ligand and the crystallographic ligand, highlighting the importance of meticulous validation and adjustment in molecular docking studies.

Table 1. Validated molecular docking

Receptors	The best gridbox sizes (Å)	RMSD (Å)
Erα	$45\times45\times45$	0,5415
PR	$40\times40\times40$	0,7415
IGF-1R	$30\times30\times30$	1,0357
VEGFR2	$40\times40\times40$	0,4632
FGFR1	$35\times35\times35$	0,3342

The determination of the active site and the size of the grid box is crucial for the validation of the molecular docking method. In this study, receptors and natural ligands were redocked ten times using grid box sizes of $30\times30\times30$ Å, $35\times35\times35$ Å, $40\times40\times40$ Å, and $45\times45\times45$ Å. Validation of the molecular docking method is achieved when the root mean square deviation (RMSD) value is less than 2 Å (Trott and Olson, 2010). RMSD serves as a quantitative metric expressing the similarity between the coordinates of two superimposed molecules, namely the natural ligands from crystallography and those resulting from redocking. A lower RMSD value indicates that the ligand's position from the redocking results closely aligns with the crystallographic results (Lopez-Comacho et al., 2019). This validation process ensures the reliability and accuracy of the molecular docking methodology employed in the study.

The molecular docking results of all test ligands against the five receptors are provided in the Supplementary Material. The enthalpy contribution to free energy serves as a valuable indicator of the specificity and strength of the interaction between the receptor and the ligand (Bronowska, 2011). These interactions encompass various types, including ionic, hydrogen bonding, electrostatic, and van der Waals interactions. Table 2 presents the Gibbs free energies of the test ligands in comparison to the control ligands.

Table 2. ΔG value of ligand-receptor complex

Ligand Code	Compound	ΔG Value (kcal/mol)					Compound Group
		ERα	PR	IGF-1R	VEGFR2	FGFR1	
P	Control ligand	-9.6[a]	-8.8[b]	-9.2[c]	-7.5[d]	-8.2[d]	Terpenoid
A	Germacrene A	-8.1	-7.9	-6.6	-7.9	-7.9	Limonoid
B	Swietenine	-7.5	-6.7	-8.1	-7.4	-8.5	Limonoid
C	3β,6-Dihydroxydihydrokarapin	-7.4	-8.9	-7.4	-8.1	-7.9	Limonoid
D	7-Deacetoxy-7-oxogedunin	-8.0	-8.0	-8.6	-7.4	-8.8	Limonoid
E	Andirobin	-7.7	-7.7	-8.5	-6.6	-8.3	Limonoid
F	3,6-O,O-Diacetylswietenolid	-7.3	-7.3	-6.2	-6.6	-8.3	Limonoid
G	Swietemahonin E	-7.6	-6.9	-6.5	-7.6	-8.1	Limonoid
H	Swietemahonin F	-8.1	-7.7	-6.8	-7.4	-8.5	Limonoid
I	Swietemahonin G	-7.4	-7.7	-7.1	-7.7	-8.0	Limonoid
J	Stigmasterol	-7.3	-8.3	-8.3	-9.5	-7.7	Steroid
K	Swietemacrofin	-7.1	-6.9	-7.0	-7.8	-8.1	Limonoid
L	7-Hidroxy-2-(4-hidroxy-3-metoxyfenil)-chroman-4-on	-8.3	-8.7	-8.2	-8.7	-9.6	Flavonoid

[a]Tamoxifen, [b]Onapristone, [c]NVP-AEW541, [d]Lucitanib

Molecular docking represents a computational technique aimed at efficiently predicting noncovalent bonds between receptors and ligands, thereby enabling the estimation of bond conformation and affinity (Trott and Olson, 2010). Employing the theory-induced fit paradigm, molecular docking considers the flexibility of both ligand and receptor to facilitate the formation of a stable ligand-receptor complex at minimal energy cost. However, due to computational constraints, this approach often utilizes a rigid receptor and a flexible ligand (Meng et al., 2011). The core principle of molecular docking, particularly when employing AutoDock Vina, involves generating a conformational ensemble of the ligand within the receptor's active site. Subsequently, these conformations are ranked based on a scoring function, which typically describes the binding energy, notably the Gibbs free energy, to assess the stability of the resulting complex (Eberhardt et al., 2021). Gibbs's free energy serves as a crucial parameter in characterizing the interaction between two compounds. A more negative Gibbs free energy value indicates a more spontaneous reaction (Nelson and Cox, 2012). In the context of receptor-ligand interaction, lower Gibbs free energy values signify more stable interactions, thereby suggesting improved inhibitory potential of the ligand against the receptor (Murray et al., 2012).

Among the 80 test ligands docked to ERα and IGF-1R, none exhibited more negative energy than the control ligand, indicating that tamoxifen and NVP-AEW541 have a higher propensity to form stable complexes with their respective receptors compared to the test ligands. Conversely, for PR, VEGFR2, and FGFR1, one, seven, and six ligands, respectively, demonstrated more negative energy values than their control ligands (**Figure 1**). This implies that these ligands have a greater propensity to interact with their receptors compared to the control ligands. Henceforth, the tested ligands demonstrating superior interaction will be referred to as selected ligand 1. Selected ligand 1 encompasses a variety of chemical groups including limonoids, steroids, flavonoids, and terpenoids. Notably, the limonoid group emerges as the predominant constituent among the selected ligands. This finding aligns with previous research conducted by Tohir et al. (2020), which demonstrated the inhibitory effect of limonoids found in S. macrophylla seeds on the growth of breast cancer cells.

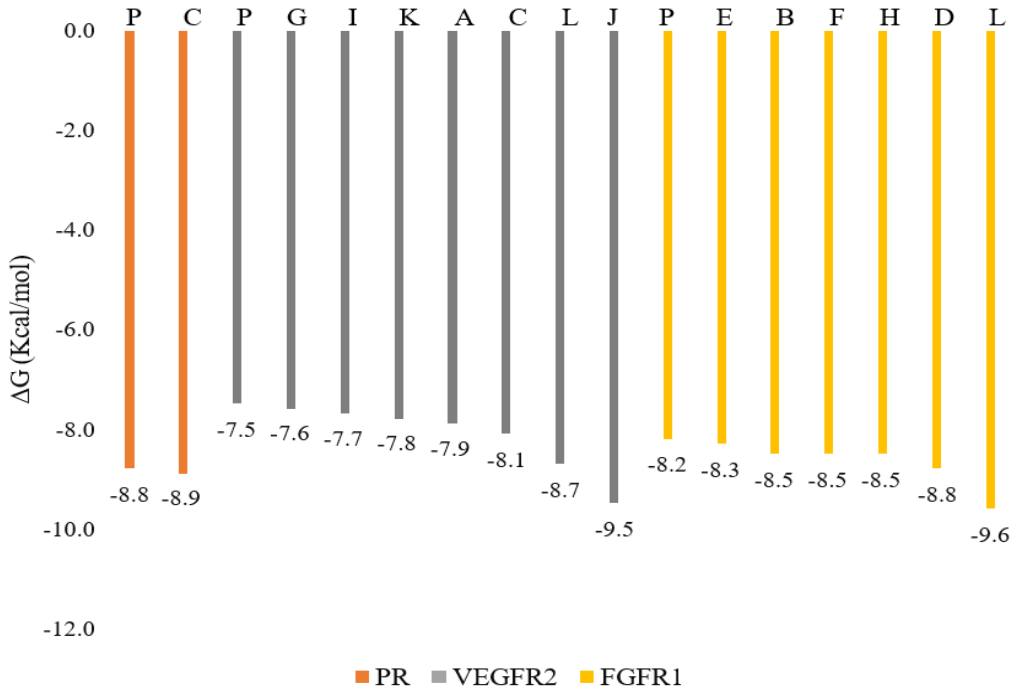

Figure 1. Selected test ligands against PR, VEGFR2, and FGFR1; ligands code see in **Table 2**

Molecular docking is widely used as a screening for drug candidate compounds. Lestari et al. (2022) conducted computational research on compounds found in black garlic to explore their efficacy against gout. Similarly, molecular docking has been utilized in the selection of compounds present in ginger essential oil for their potential as anti-acne and anti-skin aging agents, as demonstrated by Asoka et al. (2022a, 2022b). In another study, Kintamani et al. (2023) employed in silico methods to identify active compounds in andaliman essential oil with anti-skin aging properties. Furthermore, molecular docking and dynamics have been utilized by Nurlela et al. (2022) to predict the efficacy of diterpenoid kaurene compounds as specific antiviral candidates against SARS-CoV-2. Additionally, molecular docking has been extensively employed in the realm of anti-breast cancer research, albeit targeting different receptors and compounds. For instance, Dawood et al. (2020) investigated the complexation of a new pyrazole compound with VEGFR-2 for its potential anti-breast cancer activity. Acharya et al. (2019) conducted a molecular docking analysis of selected furanocoumarins against breast cancer, targeting ER-α, PR, epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR). Given the breadth of previous research utilizing molecular docking in anti-breast cancer drug development, this research has the potential to add to the repertoire of computational studies regarding the development of anti-breast cancer drugs.

2. Visualization of Ligand-Receptor Interactions

The interactions formed in the ligand-receptor complex are hydrophobic interactions, hydrogen bonds, and electrostatic interactions. Molecular docking visualization of selected test ligands 1 used the Discovery Studio Visualizer software. Visualization of the binding results was carried out to determine the interactions formed between the ligand and the receptor. The percentage of the number of amino acid residues that interact with the test ligand compared to the reference ligand is called the binding site similarity (%BSS). Ligands demonstrating a %BSS exceeding 50% were categorized as having a similar inhibition mechanism to their control ligand (Prayogo, 2021). These ligands are grouped into selected ligands 2. Among the selected ligands 2, ligands C–PR, J and L with VEGFR2, as well as L–FGFR1 exhibited a %BSS of more than 50% (**Figure 2**), indicates that these compounds share a common inhibition mechanism with their respective control ligands. Therefore, it can be inferred that these compounds exert their inhibitory effects through similar interactions as their control ligands.

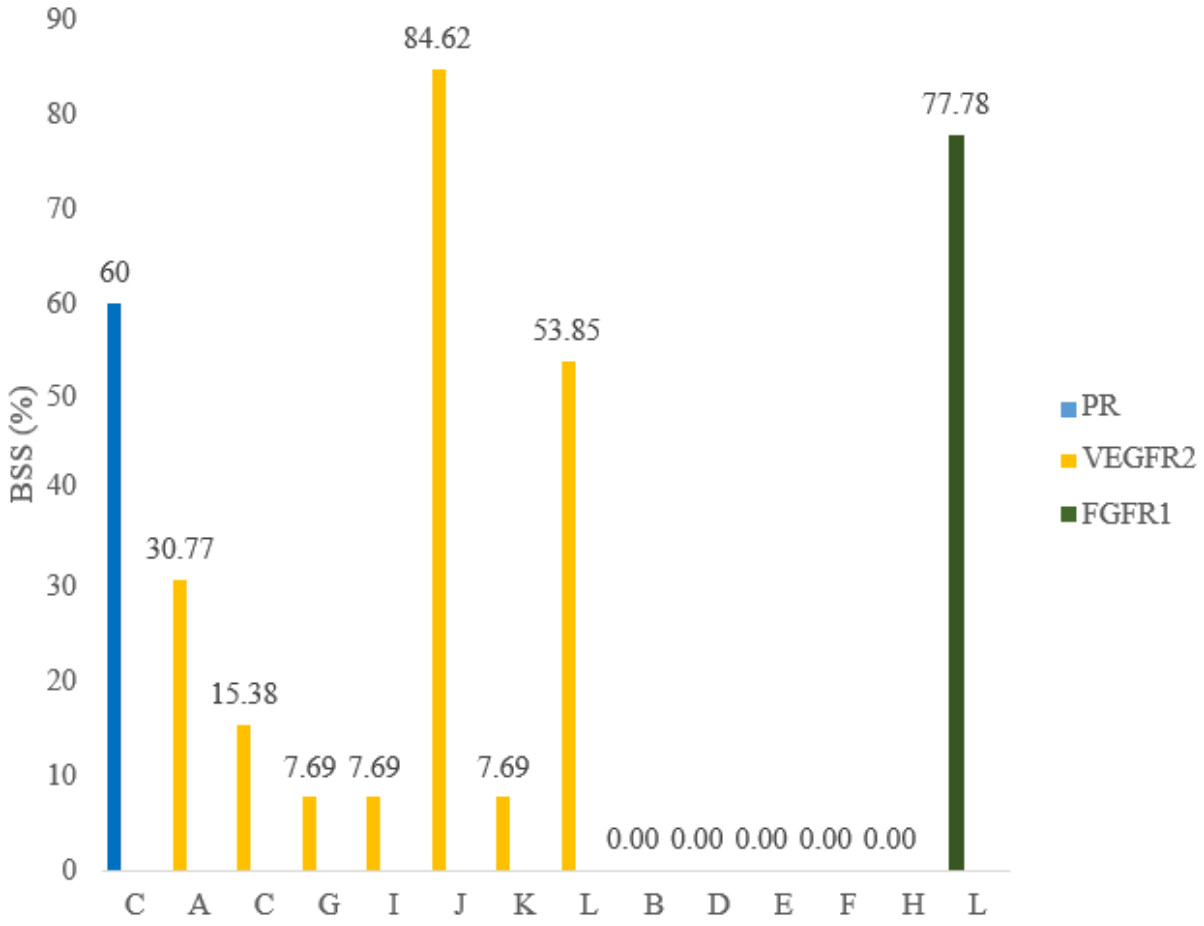

Figure 2. %BSS of selected ligands; ligands code see in **Table 2**

Ligand C exhibited a binding site similarity (%BSS) of 60.00%, indicating its ability to competitively inhibit receptors at the active site of PR with a similar inhibition interaction as its control ligand, onapristone. For ligand J, interactions with VEGFR2 yielded a %BSS of 84.62%, suggesting a high degree of similarity in the inhibition mechanism to the control ligand. Similarly, ligand L demonstrated a %BSS exceeding 50% with both VEGFR2 and FGFR1 receptors. Specifically, the visualization results indicated %BSS values of 53.85% and 77.78% for VEGFR2 and FGFR1 receptors, respectively (**Figure 2**). These findings imply that ligands J and L exhibit a similar inhibition interaction as lucitanib, likely by targeting the allosteric site of the receptor.

The significant interactions were observed between ligand C and the PR binding site. The analysis revealed the formation of strong hydrogen bonds with residues Trp765, His770, and Ile699, as well as hydrophobic interactions mediated by residues Lys769 and Pro696. Additionally, electrostatic interactions were observed via residues Arg766 and Glu695, as illustrated in **Figure 3A**. Residues marked with red circles denote those exhibiting similar interactions with the control ligand, onapristone, which demonstrated a %BSS of 60%. Notably, Arg766 has been previously reported by Kallander et al. (2010) as a residue within the PR binding site.

Figure 3B illustrates the binding pattern of FGFR1 residues with ligand J, revealing interactions through hydrogen bonds with Ala564 and Asp641, as well as hydrophobic interactions involving residues Ala512, Ala640, Val492, Phe489, Leu630, Leu484, and Lys514. These interactions highlight the potential of ligand J to engage with FGFR1 in a manner akin to its control ligand, lucitanib, as indicated by the %BBS of 84.62%. In **Figure 3C**, the binding pattern of VEGFR2 residues with ligand L is depicted, demonstrating the formation of a carbon-hydrogen bond with residue Ile1025, alongside notable hydrophobic interactions with other residues. The residues marked with red circles denote those exhibiting similar interactions with the control ligand, lucitanib, with a %BBS of 77.78%.

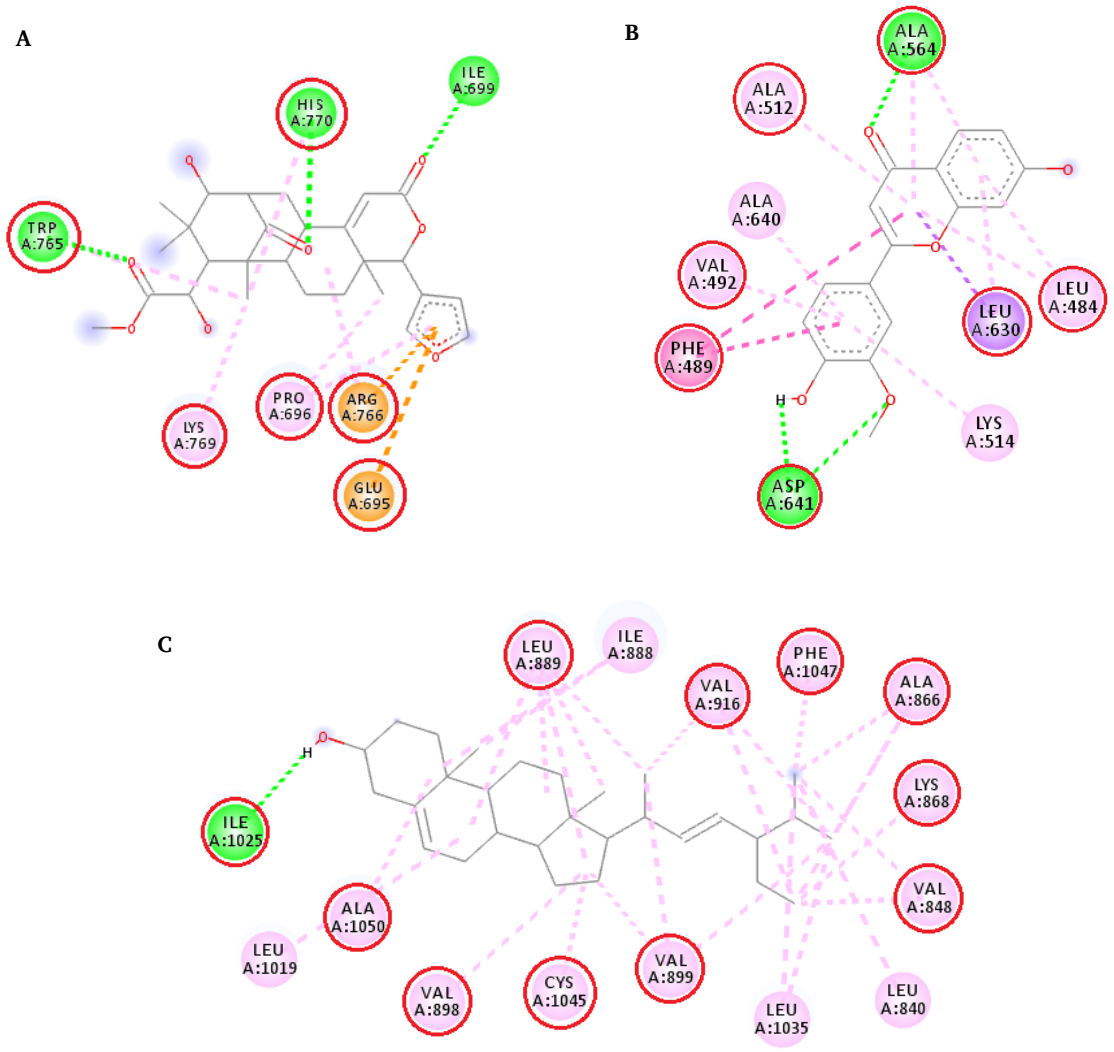

Figure 3. The interactions of ligand-protein residues (A) C-PR, (B) J-FGFR1, (C) L-VEGFR2; ligands code see in **Table 2**

Visualization of the binding results plays a crucial role in discerning the interactions between the ligand and the receptor. In particular, the presence of hydrogen bonds indicates better affinity, as evidenced by increasingly negative ΔG values (Prasetiawati et al., 2021). Electrostatic interactions arise from differences in polarity between atoms and encompass weak interactions and noncovalent bonds. Despite their weak nature, electrostatic interactions contribute significantly to stabilizing protein conformations, particularly in large quantities (Sharp and Honig, 1990). Hydrophobic interactions occur between hydrophobic groups, leading them to aggregate and minimize contact with the aqueous environment. This phenomenon aids in stabilizing the protein's globular structure by reducing the exposure of nonpolar residues to water (Lins and Brasseur, 1995).

3. Physicochemical Properties

Physicochemical analysis was carried out following Lipinski's rules. The Lipinski rule is a parameter used in screening active compounds that have the potential as drugs that are safe for oral consumption. This analysis is crucial in evaluating the nature and cytotoxicity of a compound, thereby informing key stages of drug development. Lipinski's rule considers several parameters, including molecular weight, partition coefficient, and the number of hydrogen bond donors and acceptors. All selected ligands 2 were predicted to be orally active, as they exhibited only one violation of Lipinski's rule (refer to Table 3). Notably, stigmasterol displayed a single violation, namely a log P value exceeding 5.

Table 3. Physicochemical properties of selected ligands 2

Ligand Code	Compound	log P	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Molecular Weight (g/mol)
C	3β,6-dihydroxydihydrokarapin	2,47	2	8	486,55
J	Stigmasterol	6,98	1	1	412,69
L	7-hidroxy-2-(4-hidroxy-3-metoxyfenil)-chroman-4-on	2,45	2	5	284,26

The prediction of a compound's absorption in the body relies on several parameters outlined by Lipinski et al. (2012). Specifically, a compound is deemed challenging to absorb if it exceeds five hydrogen bond donors, surpasses ten hydrogen bond acceptors, possesses a molecular weight exceeding 500 g/mol, or has a log P value exceeding 5. Conversely, a compound is considered orally active if it violates no more than one of these parameters (Sumathy et al., 2016). The log P value serves as a measure of a compound's hydrophobicity, with higher values indicating increased hydrophobicity (Widyasari et al., 2019). Compounds exhibiting excessive hydrophobicity tend to be retained within lipid bilayers, leading to prolonged retention and wider distribution, consequently increasing the risk of toxicity due to reduced selectivity in binding to target proteins. Moreover, the number of hydrogen bond donors and acceptors reflects a compound's capacity for hydrogen bonding. Compounds with higher hydrogen bonding capacity necessitate greater energy for the absorption process (Syahputra et al., 2014). Furthermore, compounds with a molecular mass exceeding 500 g/mol encounter difficulty in penetrating cell membranes via passive diffusion (Syahputra et al., 2014).

This study represents an initial step in the development of potential anticancer drugs, highlighting the need for further in vitro and in vivo testing to validate its efficacy and safety profiles. Beyond early-stage breast cancer, the findings suggest that mahogany seeds hold significant promise for the treatment of metastatic breast cancer, as well as other cancer types characterized by the expression of VEGFR2 and FGFR1.

CONCLUSION

Based on molecular binding analysis, 12 compounds have been identified as potential candidates for anticancer breast treatment. These compounds belong to various chemical groups, including limonoids, steroids, flavonoids, and terpenoids. Further analysis of ligand binding site similarity revealed that the three compounds exhibit interactions with receptors akin to their comparator drugs. The mechanism of action for 3β,6-dihydroxydihydrocarapin is predicted to involve competitive inhibition at the active site of PR. Conversely, stigmasterol and 7-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chroman-4-one are believed to inhibit allosteric sites on the receptors. Physicochemical analysis results indicate that 3β,6-dihydroxydihydrocarapin, stigmasterol, and 7-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chroman-4-one are suitable for oral consumption, suggesting their potential for further exploration in drug development processes. These findings represent significant progress in identifying promising compounds for breast cancer treatment, warranting further investigation through preclinical and clinical studies.

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