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Molecular Docking of *Michelia alba* Leaves Active Compounds Against Human Epidermal Growth Factor Receptor 2 (HER-2)

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Abstract: *Breast cancer characterized by overexpression of the human epidermal growth factor receptor-2 (HER-2) and is a deadly disease worldwide. Chemotherapy with drugs targeting HER-2 is less effective and reveals various drawbacks. This study aimed to study anticancer potential of active compounds contained in Michelia alba through molecular docking against HER-2. The molecular docking study was performed toward HER-2 receptor (PDB: 3PP0) containing 30Q native ligand with MCULE. The results show that cis-linalool oxide, trans-linalool oxide, linalool, β-elemena, α-humulene, and nerolidol contained in M. alba leaves had lower docking scores than quercetin as control. Nerolidol showed the lowest docking score among all compounds. The active compounds in the leaves of M. alba have the potential as a HER-2 inhibitor in silico.*

Key word*: anticancer, Michelia alba, molecular docking, HER-2.*

INTRODUCTION

The diagnosis and treatment of cancers have progressed rapidly; however, breast cancer is still a deadly disease worldwide (Li et al., 2019). The percentage of breast cancer patients (30%) is higher than that of cervical cancer (24%) in Indonesia. The incident of breast cancer also reaches 0.5 for every 1000 women, making it the most dangerous type of cancer in Indonesia (Ministry of Health, 2015). Human epidermal growth factor receptor-2 (HER-2) is an essential receptor in breast cancer with expression can reach 40-100 times (Krishnamurti & Silverman, 2014).

HER-2 is a receptor controlling the growth, proliferation, and repair of cells in the breast. HER-2 is a member of tyrosine kinase which can dimerize with HER-1, HER-3, and HER-4 due to the overexpression. HER-2 overexpression caused by the increasing HER-2 genes stimulates the abnormal, uncontrollable, and malignancy growth and proliferation of breast cells (Liao, 2016; Oh & Bang, 2020; Ponde et al., 2018). This overexpression is a positive HER-2 which is commonly found in breast cancer (Loibl & Gianni, 2017). Subsequently, HER-2 becomes an attractive target for breast cancer identification and treatment. Trastuzumab and pertuzumab are cancer drugs utilizing the HER-2 overexpression on the surface of cancer cells and have been reported to kill cancer cells with high selectivity/anti-HER-2 specificity. These drugs can also treat HER-2+ stage 1-3 breast cancer (Escriva et al., 2018; Pernas & Tolaney, 2019).

Furthermore, lapatinib, neratinib, and afatinib are inhibitors of tyrosine kinase and inhibit the HER-2 signaling pathway. These inhibitors bind the triphosphate to the cytoplasm of the HER-2 receptor to prevent phosphorylation and subsequent activation (Escriva et al., 2018). However, the use of these drugs in cancer chemotherapy, surgery,

and radiation therapy have shown drawbacks and adverse side effects. The relapse cases, metastasis, and resistance to treatment can also be experienced by the patients (Zhang et al., 2019). Various plants with various active compounds including *Michelia alba* have been reported to have anticancer activity.

M. alba is a flowering plant belonging to the Magnoliaceae family (Maesaroh & Ozel, 2021). This plant can be found in tropical sub-tropical areas such as China, India, Thailand, Malaysia, and Indonesia (Frodin & Govaerts, 1996). *M. alba* contains active compounds of alkaloids, benzyl, benzoic acid, and essential oils with various biological activities (Swantara et al., 2020). The essential oils of *M. alba* have been used in perfume blends (Sanimah et al., 2008; Tan et al., 2018). This plant has also been used in the treatment of bronchitis, prostatitis, and cancer (Chunqing et al., 2002; Lo et al., 2004). *M. alba* also functions as a tyrosinase enzyme inhibitor, antifungal, and antibacterial (Songsamoe et al., 2017; Chiang et al., 2012; Wang et al., 2010). However, the potential of this plant as an anticancer agent has rarely been reported. *In-silico* studies were used to identify the biological potential of the computationally active compounds. The molecular docking studies the interaction of active compounds and target proteins (Li et al., 2019; Bare et al., 2020). This study further aims to estimate the anticancer potential of the active compounds in *M. alba* leaves for breast cancer through a molecular docking study of HER-2.

RESEARCH METHODS

The molecular docking study was conducted by identifying the interaction of active compounds in *M. alba* leaves on the active side of the target protein of human epidermal growth factor receptor 2 (HER-2). Ueyama et al. (1992) reported the active compounds contained in *M. alba* leaves were *cis*-linalool oxide, *trans*-linalool oxide, linalool, β-elemene, α-humulene, and nerolidol. The HER-2 target protein (PDB ID 3PP0) in a resolution of 2.25 with native ligand 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl) phenoxy]pyridine-3-yl}amino)-5H-pyrrole[3, 2-d]pyrimide-in-5-yl]ethoxy}ethanol (03Q) was retrieved from the protein database (https://www.rscb.org/pdb). Molecular docking was performed on a Lenovo Legion-520 with an Intel® Core™ i7-7700HQ processor, CPU@2.80GHz, 8.00GB RAM, 4GB NVIDIA GeForce GTX 1050 Ti, and Windows 10 64-bit operating system.

The docking protocol was run on the MCULE one-click virtual docking containing Indigo, OpenBabel, ChemAxon, and AutoDockTools softwares (Kiss et al., 2012). The structures were prepared by converting the SMILES or InChI format from the PubChem National Center for Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/) into a two-dimensional (2D mol) structure which was further converted into a three-dimensional structure (3D mol) and stored as PDBQT. The water molecule and native ligand 03Q were deleted to prepare the target protein 3PP0. The molecular docking process was carried out at coordinates X 16,6963 Å, Y 15,9923 Å, and Z 27,1085 Å using quercetin as a control (Hashemzaei et al., 2017).

RESULTS AND DISCUSSION

cis-Linalool oxide, *trans*-linalool oxide, linalool, β-elemene, α-humulene, and nerolidol were contained in *M. alba* leaves (Ueyama et al. (1992). Molecular docking studies of these compounds against HER2 (PDB 3PP0) with MCULE gave the results as shown in Table 1. Generally, all compounds had a lower docking score than that of quercetin as control. This indicates all compounds showed inhibitory potential against HER2 *in silico*. The docking score of *cis*-linalool oxide, *trans*-linalool oxide, linalool, β-

elemena, α-humulene, and nerolidol were -6.5; -5.4; -6.4; -7.1; -5.4; -8.0, respectively. kcal/mol (Table 1). The quercetin docking score was -5.3 kcal/mol.

Tabel 1. The molecular docking results and interaction of active compounds of *M. alba* leaves on 3PP0

Complex of protein/compounds	Docking score (kkal/mol)	Hydrophobic interactions	Hydrogen bond
3PP0/*cis*-Linalool oxide	-6,5	Asp-158, Thr-157, Ser-78, Val-29, Thr-93, Val-92, Ile-62, Lys-48, Leu-80, Leu-91, Phe-159, Ala-66, Met-69	Glu-65
3PP0/*trans*-Linalool oxide	-5,4	Gly-99, Cys-100, Gly-22, Ser-23, Gly-24, Arg-144, Asn-145, Thr-157, Asp-158, Lys-48, Ala-25, Ala-46, Leu-147, Leu-21, Val-29	-
3PP0/Linalool	-6,4	Gly-24, Leu-147, Thr-93, Arg-79, Glu-65, Thr-157, Lys-48, Ala-46, Val-29, Phe-159, Lru-80, Met-69, Leu-91	Asp-158, Ser-78
3PP0/β-Elemene	-7,1	Gly-99, Thr-93, Asp-158, Thr-157, Asn-145, Ser-23, Arg-144, Gly-24, Gly-22, Cys-100, Leu-21, Val-29, Leu-147, Ala-46, Lys-48	-
3PP0/α-Humulene	-5,4	Ala-46, Gly-99, Asp-103, Gly-22, Ser-23, Arg-144, Asp-158, Gly-24, Asn-145, Thr-157, Lys-48, Leu-21, Cys-100, Leu-147, Val-29	-
3PP0/Nerolidol	-8,0	Arg-79, Asp-158, Gly-99, Cys-100, Met-96, Leu-95, Gly-24, Thr-93, Glu-65, Lys-48, Leu-80, Phe-159, Leu-91, Met-69, Val-29, Ala-46, Leu-147, Leu-21	Ser-78, Thr-157
3PP0/Quercetin	-5,3	Leu-80, Val-92, Ile-47, Leu-95, Met-96, Gly-99, Cys-100, Arg-144, Thr-157, Gly-24, Phe-159, Thr-93, Val-29, Leu-147	Leu-91, Asp-158

Nerolidol performed the lowest docking score (-8.0 kcal/mol), followed by β-elemene (-7.1 kcal/mol), *cis*-linalool oxide (-6.5 kcal/mol), linalool (-6,4 kcal/mol), and α-humulene and *trans*-linalool oxide with the similar docking score (-5.4 kcal/mol). The docking score expresses the bond strength and protein-compound interactions, which is one of the essential parameters in the virtual screening process based on structures (Maia et al., 2020). This function is responsible for predicting the binding affinity between the target protein and the compound and is the primary basis for the success or failure of the molecular docking process (Huang et al., 2010; Brink & Exner, 2009). The docking score is also valuable for determining the binding site of the compound and the conformation between the target protein and the compound (Li et al., 2013). The more negative the docking score, the stronger the protein-compound bonds and interactions (Elfiky et al., 2017).

An *in-silico* study of 265 potent monoterpenes and sesquiterpenes against 136 receptors related to hormones and women's health using Autodock revealed that nerolidol exhibits anticancer activity in silico against HER-2 receptors (PDB 3RCD) with a binding energy of 60-77% higher than the native ligand 03P. Nerolidol has also been reported to interact with dopamine receptors (PDB 3PBL) with a binding energy of 89–100% better than ETQ native ligand (Sakhteman et al., 2020). The potential of nerolidol as an antioxidant and tyrosinase inhibitor (PDB 2Y9X) with a MolDock score of -79.88 kcal/mol

has been reported (Silve et al., 2017). Furthermore, nerolidol also inhibits the HMG CoA reductase enzyme (PDB 3CCT) with a MolDock score of -90.24 kcal/mol which indicates its potential as an anti-hyperlipidemic (Mavillapalli et al., 2017).

β-Elemene possesses the endometrial anticancer activity based on *in-silico* studies using ArgusLab against protein ligase (PDB 5C5A) with a binding energy (-8.62 kcal/mol) better than the standard megestrol acetate (-6.35 kcal/mol) (Shefrin et al., 2018). β-Elemene was also reported to inhibit the protein hypoxia-inducible factor 1 subunit (HIF1A) (PDB 1H2M) *in silico* with AutoDock Tools and provided the binding energy of -5.3 kcal/mol which indicates the potential as pancreatic anticancer (Zhu et al., 2019). In addition, β-Elemene also showed antioxidant activity and were able to bind NO-protein (PDB 2CDU) and peroxiredoxin-5 (PDB 1HD2) which trigger cancer due to oxidative damage with binding energies of -6.9 kcal/mol and -4.6 kcal/mol (Alminderej et al., 2020; Farouk et al., 2021).

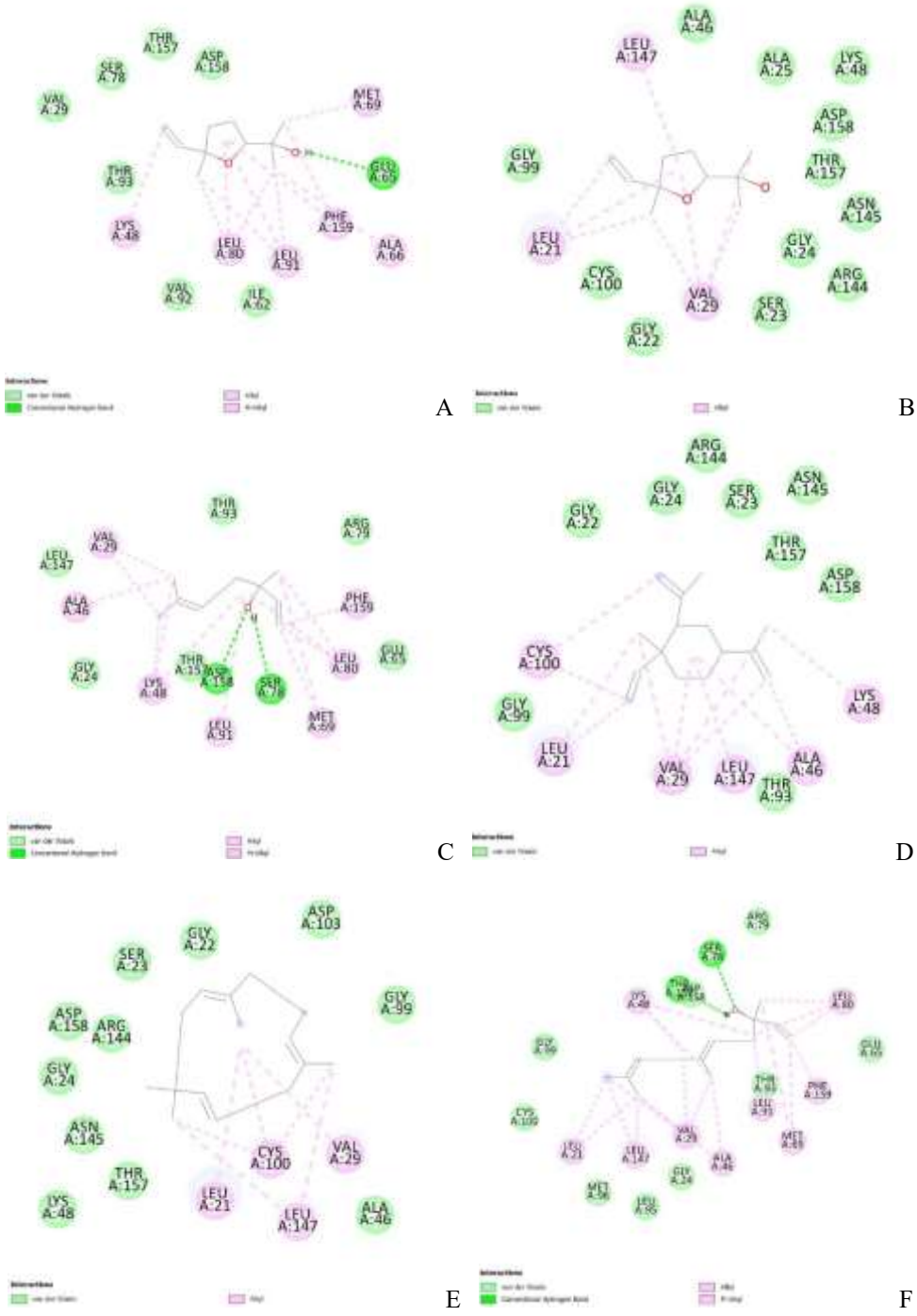
Linalool oxide has the activity against type C hepatitis virus through NS5B polymerase inhibitory pathway (PDB 4EO6) with a total energy of *cis*-linalool oxide of -60.60 kcal/mol and i-linalool oxide of -77.42 kcal/mol (Balavignesh et al., 2013). The *cis*-Linalool oxide was reported to have antioxidant activity *in silico* with a bond energy of -4.49 kcal/mol to xanthine oxidoreductase (PDB 2CKJ) (Ali et al., 2021). Linalool oxide has also been reported to have *in silico* potential as a diabetes therapeutic agent through inhibition of α-amylase (PDB 3BAJ) with a binding energy of -3.5 kcal/mol (Khamme et al., 2018).

Linalool showed its potential as a chemopreventive agent in breast cancer through *in-silico* inhibition of the SIRT2 gene (PDB 4Y6Q) with a binding energy of -4.67 kcal/mol (Bhura et al., 2019). Linalool also displayed hepatocellular carcinoma anticancer activity in HepG2 cells with a binding energy of -5.3 kcal/mol (PDB 3ELJ) (Haque et al., 2021). *In-silico* study of linalool against fructose-6-phosphate amidotransferase (GFAT) gave a bond energy value of -5.93 kJ/mol, which indicated that linalool could be used as an alternative antidiabetic (Paarakh et al., 2017).

A molecular docking study of HER-2 (PDB 3PP0) showed that α-humulene has breast anticancer activity with a binding energy of -7.50 kcal/mol (Putra et al., 2022). An *in-silico* study was also conducted to reveal the anticancer and antidiabetic activity of α-humulene which resulted in the docking score of -6.51 kcal/mol against HER-1 protein (PDB 2ITW) and of -9.09 kcal/mol against α-D-glucopyranose inhibitors (PDB 3A4A) (Devika et al., 2021). α-Humulene also has the potential as a colon anticancer agent through the inhibition of the TNF-alpha enzyme (PDB 5MU8) with a binding affinity of -16.98 kcal/mol (Singh et al., 2018). Furthermore, α-humulene also exerted a cytotoxic effect on liver cancer cells with minimal cytotoxicity against normal hepatocytes (Sotto et al., 2020).

The molecular docking results were analyzed by visualizing the interaction and bonding mode of the compound against 3PP0 (Figure 1). Table 1 and Figure 1 inform that the interaction of *M. alba* leaves active compounds with 3PP0 occurs through hydrophobic interactions and hydrogen bonds. The 3PP0–nerolidol complex with the lowest docking score (-8.0 kcal/mol) occurs via glycine-99, cysteine-100, methionine-96 residues leucine-95, glycine-24, threonine-93, leucine-80, phenylalanine-159, valine-29, and leucine-147 residues similar to the complex of 3PP0 with quercetin. The 3PP0 residues such as leucine-80, valine-92, leucine-95, methionine-96, glycine-99, cysteine-100, arginine-144, threonine-157, glycine-24, phenylalanine-159, threonine-93, valine- 29, and leucine-147 suppose to play an essential role in the interaction with *M. alba* leaves compounds. Generally, these residues play a role in hydrophobic interactions with *M. alba* leaves active compounds. Quercetin was further found to interact with leucine-91 and aspartic acid-158

residues in 3PP0 via hydrogen bonding. The 3PP0–nerolidol complex also interacts with hydrogen bonds via serine-78 and threonine-157 residues.



Gambar 1. The interaction of the active compound in *M. alba* leaves on HER-2. *cis*-Linalool oxide (A), *trans*-linalool oxide (B), linalool (C), β -elemena (D), α -humulene (E), nerolidol (F).

CONCLUSION

The active compounds of *M. alba* leaves (*cis*-linalool oxide, *trans*-linalool oxide, linalool, β-elemene, α-humulene, and nerolidol) have the potential as HER2 inhibitors in silico. The docking score of all compounds was lower than quercetin (-5.3 kcal/mol), whereas nerolidol had the lowest docking score (-8.0 kcal/mol).

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