MOLECULAR DOCKING ON BIOACTIVE COMPOUNDS OF GENISTEIN, QUERCETIN AND RESVERATROL TO BRCA1, ERA, AND EGFR RECEPTORS IN BREAST CANCER

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ABSTRAK
Kanker payudara merupakan kanker yang paling banyak dijumpai dan menjadi penyebab utama kematian akibat kanker pada wanita. Berbagai fitokimia dari bahan alam berpotensi memberikan efek terapeutik terhadap kanker payudara, beberapa diantaranya adalah genistein, quercetin, dan resveratrol. Penelitian ini bertujuan untuk mengetahui interaksi senyawa bioaktif genistein, quercetin dan resveratrol terhadap reseptor BRCA1, ERα dan EGFR pada kanker payudara secara in silico dengan molecular docking. Molecular docking dilakukan melalui beberapa tahapan mulai dari preparasi struktur 3D senyawa bioaktif, preparasi protein target, validasi metode molecular docking, dan docking senyawa bioaktif pada protein target. Semakin rendah nilai energi ikatan antara senyawa uji dengan protein target maka ikatan yang terbentuk akan semakin kuat dan stabil. Hasil docking menunjukkan nilai energi pengikatan kompleks genistein sebesar -5,04 kkal/mol dengan BRCA1, -8,85 kkal/mol dengan ERα, -7,62 kkal/mol dengan EGFR. Quercetin memiliki energi pengikatan sebesar -5,59 kkal/mol dengan BRCA1, -7,90 kkal/mol dengan ERα, dan -8,47 kkal/mol dengan EGFR. Resveratrol memiliki energi pengikatan sebesar -5,20 kkal/mol dengan BRCA1, -8,75 kkal/mol dengan ERα, dan -6,44 kkal/mol dengan EGFR. Terdapat interaksi antara senyawa bioaktif genistein, quercetin, dan resveratrol dengan reseptor BRCA1, ERα, dan EGFR pada kanker payudara, ditunjukkan dengan adanya interaksi paling selektif pada kompleks reseptor-ligan ERα dan genistein yang memiliki energi pengikatan paling rendah.

Kata kunci : genistein, kanker payudara, *molecular docking*, *quercetin*, resveratrol

ABSTRACT
Breast cancer is the most common cancer and the main cause of cancer death among women. This study aims to determine the interaction of the bioactive compounds genistein, quercetin and resveratrol on the BRCA1, ERα and EGFR receptors in breast cancer in silico with molecular docking. Molecular docking was carried out through several stages, such as preparation of the 3D structure of bioactive compound, preparation of the target protein,validation of the molecular docking method, and docking of bioactive compounds on the target protein. The lower the bond energy value between the test compound and the target protein, the stronger and more stable the bond formed. The docking results show that binding energy value of genistein complex is -5.04 kcal/mol with BRCA1, -8.85 kcal/mol with ERα, -7.62 kcal/mol with EGFR. Quercetin has a binding energy of -5.59 kcal/mol with BRCA1, -7.90 kcal/mol with ERα, and -8.47 kcal/mol with EGFR. Resveratrol has a binding energy of -5.20 kcal/mol with BRCA1, -8.75 kcal/mol with ERα, and -6.44 kcal/mol with EGFR. There is an interaction between the bioactive compounds genistein, quercetin, and resveratrol with the BRCA1, ERα, and EGFR receptors in breast cancer, indicated by the most selective interaction in the receptor-ligand complex ERα and genistein which has the lowest binding energy.

Keywords *: breast cancer, genistein, molecular docking, quercetin, resveratrol*

INTRODUCTION

Breast cancer is a malignancy in breast tissue originating from glandular epithelial cells, both ducts and lobules, and the supporting breast tissue, excluding breast skin. Malignancy in

breast cells causes breast tissue to become abnormal and proliferate uncontrollably (American Cancer Society, 2022). According to Global Observatory Cancer data in 2020, breast cancer ranks first in cancer incidence in Indonesia, namely 65,858 new cases (16.8%) of all cases and the second highest mortality, namely 22,430 cases (9.8%) of deaths found in cancer cases in Indonesia (Ferlay et al., 2021).

BRCA1 type breast cancer has a high recurrence and mortality rate.The overall risk of breast cancer is approximately 3% higher in BRCA1 mutation carriers compared with women with BRCA2 mutations (Doren et al., 2018). BRCA1 also has a high probability of mutation and duplication so research targeting this receptor continues to be developed (Ravichandran, 2017). Estrogen receptor alpha (ERα) encoded by ESR1 is an important biomarker in diagnosing breast cancer. In 60% of cases there is abnormal expression of this receptor, making the ESR1 gene an important therapeutic target (Chopra et al., 2022). One strategy for developing breast cancer drugs is through inhibiting the activity of the EGFR/HER2 kinase which plays a role in the signal transduction pathway in cell cycle regulation (Prabhavathi et al., 2022). Activation of EGFR triggers signaling pathways that result in cell proliferation, migration, invasion, and angiogenesis, namely the formation of new blood vessels to support tumor growth (Jha et al., 2022).

Over the last few years, the potential of various multitarget phytochemicals has been widely investigated, especially in natural products. This is because bioactive compounds from natural ingredients have excellent therapeutic activity with minimal toxicity (Annaji et al., 2021). Younas et al. (2018) evaluated the potential of various phytochemicals from natural ingredients that have therapeutic effects on breast cancer, some of which are genistein, quercetin, and resveratrol. These phytochemicals are predicted to suppress breast cancer proliferation through modulating various transduction and signaling pathways of genes and gene products (Younas et al., 2018).

In-silico study that can be used to predict interactions between compound ligands and therapeutic target receptors at the molecular level is molecular docking (Stanzione et al., 2021). Molecular docking is an approach that plays an important role in the discovery of new drugs. This computational drug design method is based on a mathematical algorithm by which the effective biological binding conformation between the drug and the target molecule can be evaluated (Pinzi & Rastelli, 2019).

It is important to carry out research on alternative breast cancer therapies that have specific targets and high selectivity in inhibiting the process of breast cancer metastasis. This study aims to determine the interaction of the bioactive compounds genistein, quercetin and resveratrol on the BRCA1, ERα and EGFR receptors in breast cancer in silico with molecular docking.

METHOD

The research uses an experimental study design with a computational approach which aims to determine the interaction of the bioactive compounds genistein, quercetin and resveratrol on the BRCA1, ERα and EGFR receptors in breast cancer. The data used in the research is chemical structure data of ligands and target proteins which have been screened and accessed via PDB and PubChem.

Compound screening is carried out by inputting canonical SMILES information for each compound on the SwissADME and Way2Drug servers. This screening aims to predict the ADMET (absorption, distribution, metabolism, excretion and toxicity) and QSAR (Quatitative Structure-Activity Relationship) potential of the compounds under study. Preparation is done by changing the structure format used to. pdbqt. Then redocking of the native ligand is carried out to determine the exact location of the active site of the receptor which is presented in the

form of gridbox parameters. The ligand is docked into the target structure using the AutoDock4 system with grid box values obtained from the results of redocking the native ligand. The docking process carried out is semi-flexible, because the receptor used is rigid while the ligand is flexible. Docking results are evaluated to identify the lowest binding energy and calculate the inhibition constant of the interaction. Protein-ligand complexes were visualized using Discovery Studio software. Using this software, polar and hydrophobic interactions between ligands and targets are characterized and 2D and 3D illustrations of these interactions are generated.

This research has been granted approval from The Ethics Commission Faculty of Medicine, Sriwijaya University (Protocol No: 335-2023).

Table 1. Coordinate Value and Grid Box Sizes

	BRCA1	ERα	EGFR
Center (Å)			
x	-8,049	5,884	21,697
y	24,566	5,698	0.303
z	38,302	29,805	52,093
Box dimension (Å)			
x	48	40	42
y	48	40	40
z	48	40	40

Table 2. Binding Energy Result of Docking

Receptor-Ligand Complex		*Binding Energy*(kcal/mol)
BRCA1	Genistein	-5.04
	Quercetin	-5.59
	Resveratrol	-5.20
ERα	Genistein	-8.85
	Quercetin	-7.90
	Resveratrol	-8.75
EGFR	Genistein	-7.62
	Quercetin	-8.47
	Resveratrol	-6.44

RESULT

Results of redocking carried out using Autodock4 on the target receptors BRCA1, ERα, and EGFR with their respective native ligands to determine the exact location of the active site of the receptor. The lowest RMSD from redocking each native ligan are 1.16 Å on ERα-ztw complex structure, 1.55 Å on EGFR-aq4 complex structure, and 2.75 Å on BRCA1-sep complex structure. Information on the location of the active site is in the form of grid box parameters which are presented in table 1.

Molecular docking between target receptors and potential ligands is carried out using AutoDockTools with the AutoDock4 system. Gridbox parameters are adjusted to the redocking result information. After docking, the binding energy values obtained from the docking results of each target receptor and ligand are shown in table 2.

ISSN : 2774-5848 (Online)
ISSN : 2777-0524 (Cetak)

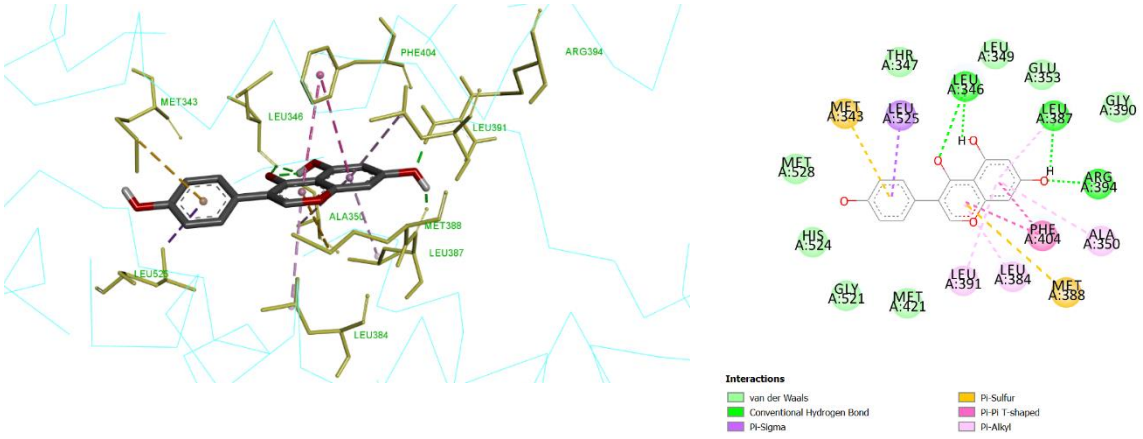

Figure 1. Visualization of Erα-Genistein Complex Interactions

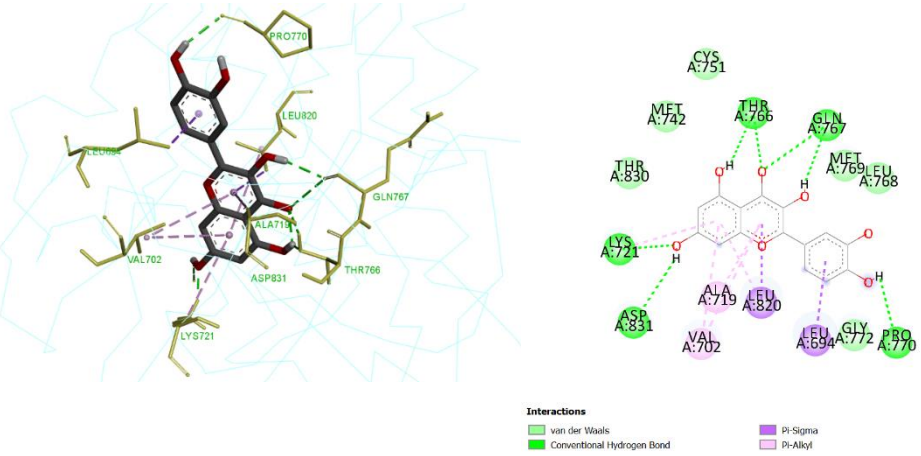

Figure 2. Visualization of EGFR-Quercetin Complex Interactions

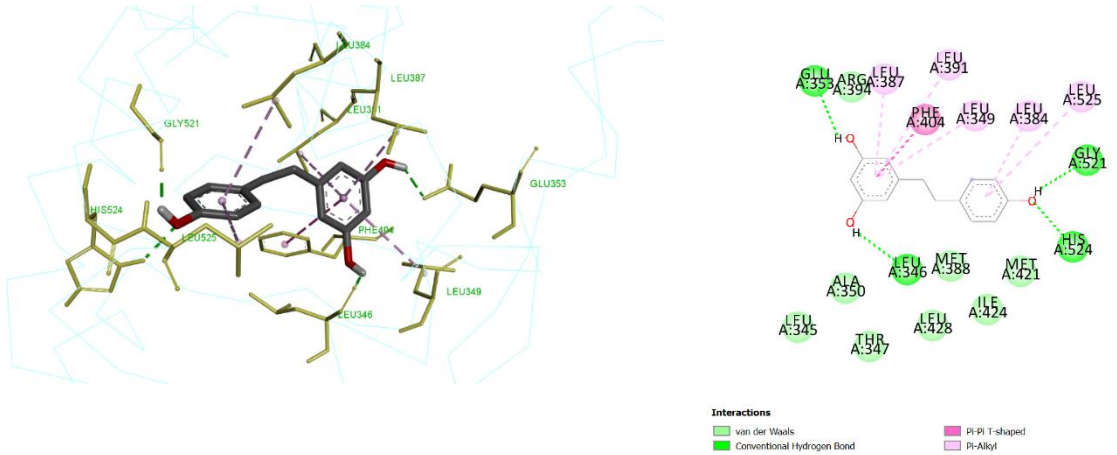

Figure 3. Visualization of Erα-Resveratrol Complex Interactions

DISCUSSION

According to Lipinski's rule of five (RO5), a substance has poor solubility and permeability if a substance violates more than one of the four existing criteria. These criteria include a molecular mass of less than 500 daltons, lipocity (LogP) ≤5, donor hydrogen bonds ≤5, acceptor hydrogen bonds ≤10, and molar refractivity between 40-130. Lipinski's rule of five was evaluated by online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). On the other hand, a substance is considered to have good solubility and permeability if the substance does not violate or only violates one of these four criteria. Based on druglikeness screening on SwissADME and Way2Drug servers, it is known that the three potential compounds do not have RO5 violations. Therefore, it can be concluded that genistein, quercetin, and resveratrol have good solubility and permeability and have potential if they are to be used as oral drugs. The results found regarding the number of violations of Lipinski's Rule of Five in this study are in line with previous research. In research by Akash et al. (2023), it was found that genistein had no violations in any parameters (Akash et al., 2023). Research by Bhowmik et al. (2021) and Chandran et al. (2023) states that quercetin meets the Lipinski Rule of Five criteria. The ADMET properties of quercetin also show good permeability through membranes (Bhowmik et al., 2021); (Chandran, 2023) . In the research by Adelusi et al. (2021) it was also stated that resveratrol passed tests for physicochemical properties and ADMET studies by fulfilling Lipinski's Rule of Five for each parameter (Adelusi et al., 2021).

The protein structure utilized must meet certain criteria, including having a resolution lowest than 3Å, as it relates to the protein sequencing upon its formation. The higher resolution of the protein, the lower its Armstrong resolution value, indicating that the captured depiction during the protein sequencing is more specific. The other criteria is, the structure must have no mutations (de Azevedo, 2019). But, on this research we used BRCA1 structure with mutation to suit the needs of research targeting genes in breast cancer. The lowest RMSD from redocking each native ligan are 1.16 Å on ERα-ztw complex structure, 1.55 Å on EGFR-aq4 complex structure, and 2.75 Å on BRCA1-sep complex structure. Recommended limit for RMSD value for the result structure from redocking and docking complex protein-ligands in molecular docking is 2.0 Å (de Azevedo, 2019). Value for redocking native ligan ER-alpha and EGFR below the recommended limit of 2.0 Å, meanwhile value for redocking native ligan BRCA1 is a little high than the recommended limit. This can happen because BRCA1 structure we used has mutations and has a smaller ligand than other structures.

After docking between genistein and each target receptor, it was found that genistein had the highest and most selective interaction with ERα target receptors with binding energy -8.85 kcal/mol, followed by EGFR with binding energy -7.62 kcal/mol and BRCA1 with binding energy -5.04 kcal/mol. In this study, the results showed that genistein has the lowest binding energy value among other receptor-ligand complexes and is the most selective for the target receptor ERα. These results are in line with research that has been conducted previously. In research by Liu et al. (2023), the binding energy of genistein for estrogen receptor alpha (ERα) was reported to be -7.3 kcal/mol (Liu et al., 2023). There is a difference in binding energy values in this research and previous research due to the different docking systems used where previous research used the AutoDockVina system.

After docking between quercetin and each target receptor, it was found that quercein had the highest and most selective interaction with the EGFR target receptor with binding energy -8.47 kcal/mol, followed by ERα with binding energy -7.90 kcal/mol and finally BRCA1 with binding energy -5.59 kcal/mol. In this study, it was found that EGFR had the highest binding energy interaction with quercetin, valued at -8.47 kcal/mol. These results are in line with research by Omoboyede et al (2023) who carried out molecular docking of the quercetin

compound against the EGFR receptor in prostate cancer (Omoboyede et al., 2023). In this study, it was found that quercetin had a binding energy value of -8.7 kcal/mol. This indicates that quercetin has good binding energy with EGFR and shows potential interaction with this target.

After docking between resveratrol and each target receptor, it was found that resveratrol had the highest and most selective interaction with ERα target receptors with a binding energy of -8.75 kcal/mol, followed by EGFR with binding energy -6.44 kcal/mol and BRCA1 with a binding energy -5.20 kcal/mol. These results are consistent with research by Annaji et al. (2021) which states that resveratrol has estrogenic activity, namely functioning as an ERα estrogen receptor agonist or ligand antagonist at very low concentrations (Annaji et al., 2021). Researchers could not find previous studies that examined the binding energy of resveratrol on BRCA1 and ERα. However, some pertinent information can be inferred from the available research. In research by Sahu et al. (2022), resveratrol was found to increase BRCA1 expression which binds to the promoter region of the BRCA1 gene. These findings suggest that resveratrol may interact with BRCA1 and related proteins (Sahu et al., 2022).

The higher the affinity of a drug for a target protein, the lower drug concentration will be required to reach the highest saturation. The strongest binding affinity is indicated by the smallest binding energy in kcal/mol units. Therefore, the smaller the binding energy value, the more stable the interaction between the ligand and the target protein, and the higher the affinity (Jin et al., 2021). This is consistent with the results of research by Yen et al. (2022) which shows that the combination of using natural ingredients including genistein and quercetin, with tamoxifen produces synergistic anticancer effects, including increased inhibition of tumor cell growth and tamoxifen sensitivity as well as reduction of side effects or toxicity of tamoxifen (Yen et al., 2022).

Visualization of interactions between ligands and receptors is important for understanding intramolecular interactions and intermolecular interactions in receptor-ligand complexes in more detail. Hydrogen bonds are noncovalent interactions that occur between donor hydrogen atoms (with electrons) and acceptor hydrogen atoms (receiving electrons). These hydrogen bonds have a lower bond energy than van der Waals interactions, but are sufficient to maintain the structure of the protein and ligand in interaction. Van der Waals forces are noncovalent weak interactions that occur between atoms that are far away from each other. Van der Waals forces influence the interactions between donor and acceptor molecules in protein-ligand structures by obtaining nonspecific weak attractive interactions that influence protein structure and stability. In the context of molecular docking, hydrogen and van der Waals interactions influence the stability of the protein-ligand conformation after docking (de Azevedo, 2019).

In this study, the most selective target receptor for the genistein compound was ERα. This can be seen in the results of the interaction of the ERα and genistein complex (Figure 1) which shows the existence of molecular and intermolecular interactions, characterized by the formation of three hydrogen bonds and eight van der Waals forces. These results are consistent with two studies that have been conducted previously. Research by Wang et al. (2021) shows that genistein interacts with ERα, and genistein's affinity for ERα was found to be different from other isoflavone phytoestrogens such as daidzein and formononetin (Wang et al., 2021). In addition, genistein was found to interact more easily with both estrogen receptors compared to 17β-estradiol, as shown by docking and binding energy analysis in the research of Yuseran et al. (2019). These findings suggest that genistein has the potential to bind to ERα, highlighting its possible role in modulating estrogen receptor activity (Yuseran et al., 2019).

The most selective target receptor for the quercetin compound is EGFR. This can be seen in the results of the interaction of the ERα and genistein complex (Figure 2) which shows the existence of molecular and intermolecular interactions, characterized by the formation of five hydrogen bonds and six van der Waals forces. Molecular docking studies have revealed that

quercetin forms hydrogen bonds with specific amino acid residues of EGFR, indicating its potential role in modulating EGFR activity. These findings support the theory that quercetin can interact effectively with EGFR, highlighting its potential as a therapeutic agent in conditions involving EGFR dysregulation (Omoboyede et al., 2023).

In this study, the most selective target receptor for the resveratrol compound was ERα. This can be seen in the results of the interaction of the ERα and resveratrol complex (Figure 3) which shows the existence of molecular and intermolecular interactions, characterized by the formation of five hydrogen bonds and six van der Waals forces. This is consistent with the research results of Sahu et.al. (2022) research on MD simulations for 100 picoseconds shows that resveratrol (E2) contributes to the formation of four stable hydrogen bonds with key ER-alpha pocket residues: Arg394, Glu353, His524, and Leu525. In addition, docking results and MD simulations also show that resveratrol increases BRCA1 gene expression and interacts with MBD (Methyl-CpG Binding Domain) family proteins with significant binding affinity, especially towards MeCP2 protein. This interaction is supported by the formation of strong hydrogen bonds between resveratrol and the MeCP2 protein. Therefore, the docking results indicate that resveratrol has the potential to interact with ER-alpha receptors and MBD family proteins through hydrogen bonds and van der Waals forces, which may influence genetic regulation and related signaling pathways.

CONCLUSION

Based on analysis carried out using a computational approach, it is known that there is an interaction between the bioactive compound genistein and the BRCA1, ERα, and EGFR receptors in breast cancer, indicated by the most selective interaction at the ERα receptor, followed by EGFR and BRCA1. There is an interaction between the bioactive compound quercetin and the BRCA1, ERα, and EGFR receptors in breast cancer, shown by the most selective interaction at the EGFR receptor, followed by ERα and BRCA1. Also, there is an interaction between the bioactive compound resveratrol and the BRCA1, ERα, and EGFR receptors in breast cancer, shown by the most selective interaction at the ERα receptor, followed by EGFR and BRCA1. The interaction results in this research are still rigid, so further research is needed, such as molecular dynamics simulations, to see the movement of atoms and molecules from interactions between proteins and ligands.

ACKNOWLEDGEMENT

We would like to express our deepest gratitude to all parties who have contributed to this research. Thank you to our colleagues who have provided advice, support, and inspiration throughout the research process. We also want to thank all the participants and respondents who took the time to participate in this study. Additionally, we extend our thanks to the institutions that have provided support and facilities for conducting this research. All contributions and assistance have been immensely valuable for the smooth execution and success of this study. Thank you for all the hard work and collaboration that have been established.

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