BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 14, Number 1, April 2025 | Pages: 199-204 | DOI: 10.14421/biomedich.2025.141.199-204 ISSN 2540-9328 (online)

Prediction of *Artocarpus altilis* Potential as an Anti Breast Cancer by Inhibiting EGFR: a Molecular Docking Study

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Manuscript received: 18 January, 2025. Revision accepted: 15 May, 2025. Published: 13 June, 2025.

Abstract

Epidermal Growth Factor Receptor (EGFR) is an important target in breast cancer therapy, given its role in tumor cell proliferation, motility, and invasion through critical signaling pathways such as Ras-MAPK and PI3K/Akt. This study explored the potential of *Artocarpus altilis* (AA) active compounds, which are rich in flavonoids, as an alternative to chemotherapy. The molecular docking method was used to predict the interaction between AA compounds and EGFR protein (PDB ID: 2J6M). Docking validation showed an RMSD value of 0.854 Å, indicating high accuracy. Ellagic acid showed the best binding affinity (-8.4 kcal/mol), followed by Quercetin (-7.3 kcal/mol), Catechin, and Epicatechin (-7.2 kcal/mol). Residue analysis revealed that MET793 plays a key role in the stability of the interaction. Interaction visualization and ADMET prediction showed that most of the compounds fulfilled Lipinski's Rule of Five, with no risk of hepatotoxicity or mutagenesis. Potential compounds such as Quercetin and Epicatechin showed comparable performance to doxorubicin, but with lower potential side effects. These results strengthen the role of natural compounds as candidates for EGFR-targeted cancer therapy, providing a basis for the development of safer and more effective anticancer drugs.

Keywords: Breast cancer; EGFR; *Artocarpus altilis*; Molecular docking.

INTRODUCTION

Breast cancer is a global problem to this day, data shows that this disease was experienced by 11.7% of the world's population in 2020. (Sung et al., 2021)The development of breast cancer through several pathways, one of which is the epidermal growth factor receptor (EGFR) which is stimulated by Epidermal Growth Factor (Wilson et al., 2009). Treatment for Breast cancer involves multidisciplinary science including surgery, radiotherapy, neoadjuvant and adjuvant (Di Nardo et al., 2022). Treatment with chemotherapy is the main choice that is still often used today. However, the long-term side effects that arise can include fatigue, insomnia, peripheral neuropathy, cognitive impairment, cardiotoxicity to triggering the emergence of other malignancies (Goedendorp et al., 2012; Zamorano et al., 2016).

Breadfruit (*Arthocarpus altilis*) belongs to the *Moraceae family* which is widely used by the community as a traditional medicine (Ganeson et al., 2018). The largest content of AA is flavonoids, flavonoids have strong anticancer properties that function as antioxidants in normal cells and as pro-oxidants in cancer cells that trigger oxidative stress and induce apoptosis, mainly due to the content of artocarpin (Jantapaso & Mittraparp-Arthorn, 2022). Flavonoids show anti-metastatic effects by inhibiting migration, invasion of cancer cells, and angiogenesis through modulation of important signaling pathways such as NF-κB, AP-1, p53, and PI3K/Akt (Aswathy et al., 2024). Flavonoids in AA can affect epigenetic mechanisms, such as DNA methylation and histone modifications, making them important candidates for cancer prevention and therapy (Sitarek et al., 2024).

Molecular docking is a method to predict how ligands interact with receptor proteins, as well as assess their binding affinity and determine the optimal conformation and orientation of the ligand when interacting with the target protein (Meng et al., 2011). Molecular docking works at the atomic level to understand the interaction process of small molecules at the target protein binding site. (Agu et al., 2023). The docking process often uses molecular mechanics to quickly evaluate ligand conformation, match the 3D shape of the ligand with the target, or use hybrid methods to obtain more accurate predictions (Soleymani et al., 2022). This study aims to predict the potential of AA as an anti-breast cancer through the EGFR receptor through molecular docking studies.

MATERIALS AND METHODS

Preparation of test receptors and ligands

This study used the EGFR protein with PDB ID: 2J6M obtained through https://www.rcsb.org/. This protein has been used previously in studies that have the potential for interaction with breast cancer (Acharya et al., 2019). The protein repair process is carried out to separate the protein chain from other molecules such as natural ligands, water, and cofactors (Syahputra et al., 2022). This process uses pymol software to find a more specific sequence. The active compound Artocarpus altilis became the test ligand in this study, the structure of each compound was obtained through https://pubchem.ncbi.nlm.nih.gov/. The active compounds used are: caffeic acid (689043), chlorogenic acid (1794427), coumaric acid (637542), ferulic acid (445858), hyperoside (5281643), quercetin (5280343), ellagic acid (5281855), gallic acid (370), catechin (9064), Epicatechin (72276), limonene (22311), γ-terpinene (481107192), terpinolene (11463), and doxorubin (31703) as standard drugs.

Molecular docking simulation

The docking method must be validated using several methods, one of which is the redocking process (Dallakyan & Olson, 2015). This redocking process has parameters that will show the ligand deviation that occurs during the docking process. The validity parameter of the method is the root mean square deviation (RMSD) with a maximum value of less than 2 Å, the lower the value, the better. This process is needed to determine the location and size of the grid box (X, Y, Z) of the native ligand, as a reference in specific docking (Dai et al., 2018). The redocking process uses the vina tool as a docking process runner in the pyrx application. The open babel tool in pyrx is used as a converter of ligand and receptor files to PDBQT. This tool is also used to minimize the energy of each compound in order to obtain the lowest energy of the compound during the docking process. The docking simulation process uses the same method by adjusting the location and size of the native ligand grid box. Evaluation of the docking results in the form of binding affinity formed during the docking simulation process. Low binding affinity indicates good interaction ability of the ligand with the protein (Hassan et al., 2020).

Visualization of results

The results of the redocking process were calculated using RMSD and visualized the overlap between the ligand before and after the docking process using pymol software and biovia discovery studio 2021. (Lestariningrum et al., 2024)Visualization of the docking results was used as an analysis of the interaction of amino acid residues formed between the ligand and the receptor. Visualization of amino acid interactions using the ligplus application which shows the hydrogen and non-hydrogen bonds formed (Afladhanti et al., 2023).

Prediction of pharmacokinetics, toxicity and physicochemistry of test compounds

Pharmacokinetic and toxicity predictions use ADMET parameters that can be accessed through https://biosig.lab.uq.edu.au/pkcsm/prediction. This prediction requires Canonical SMILES for each compound as an analysis format obtained through https://pubchem.ncbi.nlm.nih.gov/. Physicochemical predictions can be accessed through http://www.swissadme.ch/index.php by ensuring Canonical SMILES for each compound. The parameters used in physicochemical predictions are Lipinski rules which are common parameters used in the development of a new oral drug (Dong et al., 2018).

RESULTS AND DISCUSSION

Docking Analysis

The validation results of the docking method using PyRx showed that the root mean square deviation (RMSD) value reached 0.854 Å, indicating the high accuracy of the docking model used (Dallakyan & Olson, 2015). The validation results of the docking method using PyRx showed that the root mean square deviation (RMSD) value reached 0.854 Å, which is far below the maximum limit of less than 2 Å, indicating the high accuracy of the resulting docking model. This process is important to determine the position and size of the grid box (X, Y, Z) of the original ligand as a reference for specific docking to the target protein. This analysis shows that the ligand structure has been well integrated into the active site of the target protein, with the center position of the grid box at coordinates x = -52.555, y = 0.208, and z = -19.899, and the grid box sizes are x = 13.673, y = 11.664, and z = 21.900, respectively. This information is very important to continue the specific docking steps, ensuring that the simulation is carried out in the right area.

In addition, molecular docking analysis revealed that the active compounds from Artocarpus altilis have good affinity values for the target protein, as listed in Table 1 of the analysis results. The results of the molecular docking analysis showed that ellagic acid was the ligand with the highest affinity for the target protein, with a ΔG value of -8.4 kcal/mol. This finding confirms the potential of caffeic acid as a potent therapeutic agent, capable of interacting effectively with the target protein. Quercetin showed good interaction, after that of ellagic acid with a ΔG value of -7.3 kcal/mol. This potential is reinforced by the low ΔG value, indicating that caffeic acid and quercetin can significantly inhibit EGFR protein activity, making them attractive candidates in the development of new drugs. This indicates that although their affinity is lower than ellagic acid, both still have potential as alternatives in the treatment of this protein.

For comparison, doxorubicin, which has a ΔG value of -6.6 kcal/mol, serves as a control in this analysis.

Table 1. Docking Analysis Results.

Compound	Binding Affinity
Native ligand	-9.5
Caffeic acid	-5.6
Chlorogenic acid	-6.7
coumaric acid	-5.4
Ferulic acid	-5.5
Hyperoside	-6.7
Quercetin	-7.3
Ellagic acid	-8.4
Gallic acid	-5
Catechin	-7.2
Epicatechin	-7.2
Limonene	-5
Γ-terpinene	-5.1
Terpinolene	-5.2
Doxorubin	-6.6

Visualization of the interaction of amino acid residues of natural ligands (A), Doxorubicin (B), Ellagic acid (C), and Quercetin (D) with EGFR protein is shown in Figure 1. The results of molecular docking analysis indicate that the amino acid residue MET793 plays an important role in the formation of hydrophobic bonds, which shows a significant contribution to the stability of the interaction between the ligand and the target protein. These findings strengthen the understanding of the mechanism of ligand interaction with EGFR, as well as the potential of natural compounds in the development of targeted therapies.

Analysis of the interaction of amino acid residues formed from the native ligand in Figure A shows the presence of hydrogen bonds between MET793 and an interaction distance of 3.20 Å. In addition, there are five dominant non-hydrogen bonds involving amino acid residues ALA743, Pro794, LEU781, GLY796, and LEU844. The existence of these bonds indicates that MET793 plays a key role in the stability of ligand interactions with EGFR proteins, as well as contributing to the efficiency of ligand binding (Radwan et al., 2024). Doxorubicin, as a control drug in this study, showed that the amino acid residue PRO794 also formed hydrogen bonds with EGFR. In addition, there are seven dominant non-hydrogen bonds involving residues ALA743, MET793, LEU781, GLY796, ASP855, LEU792, and LEU844. This indicates that Doxorubicin is able to interact in a complex with the active site of EGFR, which has the potential to increase its effectiveness as a therapeutic agent (Ibrahim et al., 2020).

Ellagic acid, which has the lowest binding energy value, shows three hydrogen bonds with MET793, MET793, and LYS745 as non-dominant bonds. In addition, four non-hydrogen bonds were found involving residues ALA743, ASP855, LEU792, and LEU844. This shows that although Ellagic acid has a low binding energy, the interactions formed are still quite significant and can contribute to the anticancer potential of this compound. Quercetin forms three hydrogen amino acid residue interactions, namely with ASP855, MET793, and Pro794. This interaction shows that Quercetin also has the potential to bind the EGFR protein efficiently, similar to other compounds. The combination of various amino acid residue interactions in the test ligand shows the complexity and strength of the interaction similar to the control drug, so that in the future it can be further explored for the development of natural compound-based therapies that are more effective and have minimal risk of toxicity (Amelia et al., 2022).

ADMET Analysis

All compounds have molecular weights below 500. Log P (< 5) All compounds meet the log P criteria, indicating adequate lipophilicity (Table 2). Hydrogen Bond Donors (HBD < 5) The majority of compounds meet the HBD criteria. Compounds that exceed the threshold are Chlorogenic acid (6 HBD) and Hyperoside (8 HBD), which can affect membrane permeability. Hydrogen Bond Acceptors (HBA < 10) All compounds meet the HBA criteria except Hyperoside, which has an HBA value of 12, above the threshold. Not all compounds show hepatotoxic properties and therefore do not pose a risk for clinical application. All compounds have no mutagenic potential based on the Ames test (Guan et al., 2018).

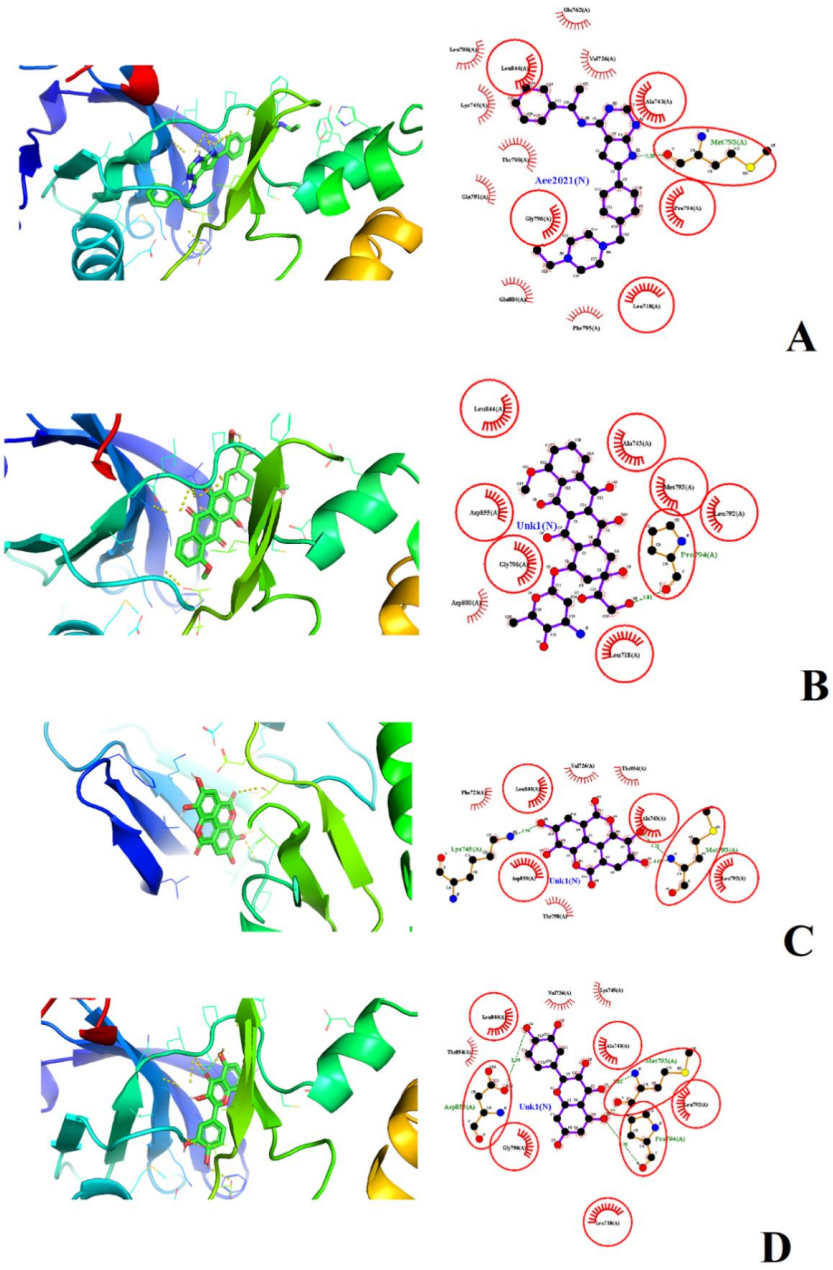

Figure 1. Visualization of Amino Acid Interactions Between Proteins and Ligands (A. Native Ligand, B. Doxorubicin, C. Ellagic Acid, D. Quercetin).

Table 2. Physicochemical Analysis and Toxicity.

Compound	MW (<500)	Log P (<5)	HBD (<5)	HBA (<10)	Hepatotoxicity	Ames Mutagenesis
Caffeic acid	180.16	1.09	3	4	No	No
Chlorogenic acid	354.31	0.75	6	9	No	No
coumaric acid	164.16	1.38	2	3	No	No
Ferulic acid	194.18	1.39	2	4	No	No
Hyperoside	464.38	0.54	8	12	No	No
Quercetin	302.24	1.99	5	7	No	No
Ellagic acid	302.19	1.31	4	8	No	No
Gallic acid	170.12	0.50	4	5	No	No
Catechin	290.27	1.22	5	6	No	No
Epicatechin	290.27	1.22	5	6	No	No
Limonene	136.23	3.31	0	0	No	No
Γ-terpinene	136.23	3.31	0	0	No	No
Terpinolene	136.23	3.45	0	0	No	No

CONCLUSION

Ellagic acid has the highest binding affinity (-8.4 kcal/mol), followed by Quercetin (-7.3 kcal/mol), Catechin, and Epicatechin (-7.2 kcal/mol). Interaction of amino acid residues, such as MET793, provides stability in ligand binding. Pharmacokinetically, compounds such as Ellagic acid and Quercetin show good profiles according to Lipinski's rule, with no indication of hepatotoxicity or mutagenesis.

Acknowledgement: The authors declare that there is no conflict of interest in this research and this research did not receive funding from any source. All relevant information has been provided in this article.

Competing Interests: The authors declare that there are no competing interests.

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