narra j

Short Communication

Molecular interaction analysis of ferulic acid (4-hydroxy-3-methoxycinnamic acid) as main bioactive compound from palm oil waste against MCF-7 receptors: An in silico study

Mochammad A. Herdiansyah[1], Rafli Rizaldy[2], Mochamad RT. Alifiansyah[3], Amelia JT. Fetty[2], Dhea Anggraini[4], Niken Agustina[2], Fariz R. Alfian[2], Primanita NM. Setianingsih[1], Verah Elfianah[1], Halimatus S. Aulia[1], Justitia ERP. Putra[1], Arif NM. Ansori[5,6,7], Viol D. Kharisma[1,7], Vikash Jakhmola[6], Hery Purnobasuki[1], Intan A. Pratiwi[1], Maksim Rebezov[8,9], Svetlana Shmeleva[10], Tatyana Bonkalo[11,12], Dmitriy F. Kovalchuk[12] and Rahadian Zainul[13,14]*

[1]Department of Biology, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia; [2]Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia; [3]Department of Pharmaceutical, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia; [4]Department of Practical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia; [5]Postgraduate School, Universitas Airlangga, Surabaya, Indonesia; [6]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India; [7]Virtual Research Center for Bioinformatics and Biotechnology, Surabaya, Indonesia; [8]Department of Scientific Research, V. M. Gorbatov Federal Research Center for Food Systems, Moscow, Russian Federation; [9]Faculty of Biotechnology and Food Engineering, Ural State Agrarian University, Yekaterinburg, Russian Federation; [10]Moscow State University of Technologies and Management (The First Cossack University), Moscow, Russian Federation; [11]Research Institute for Healthcare Organization and Medical Management, Moscow Healthcare Department, Moscow, Russian Federation; [12]Kuban State University, Krasnodar, Russian Federation; [13]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, Padang, Indonesia; [14]Center for Advanced Material Processing, Artificial Intelligence, and Biophysic Informatics (CAMPBIOTICS), Universitas Negeri Padang, Padang, Indonesia

*Corresponding author: rahadianzmsiphd@fmipa.unp.ac.id

Abstract

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phytochemical compound that is commonly found in conjugated forms within mono-, di-, polysaccharides and other organic compounds in cell walls of grain, fruits, and vegetables. This compound is highly abundant in the palm oil waste. The aim of the study was to predict the anticancer activity of ferulic acid against the breast cancer cell lines (MCF-7) receptors through a computational analysis. MCF-7 receptors with PDB IDs of 1R5K, 2IOG, 4IV2, 4IW6, 5DUE, 5T92, and 5U2B were selected based on the Simplified Molecular Input Line Entry System (SMILES) similarity of the native ligand. Thereafter, the protein was prepared on Chimera 1.16 and docked with ferulic acid on Autodock Vina 1.2.5. The ligand-protein complex interaction was validated by computing the root mean square fluctuation (RMSF) and radius of gyration (Rg) through molecular dynamic simulation. In addition, an absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction was performed on ferulic acid using the pkCSM platform. The molecular docking revealed that the ferulic acid could interact with all receptors as indicated by the affinity energy <-5 kcal/mol. The compound had the most optimum interaction with receptor 2IOG (affinity energy=-6.96 kcal/mol), involving hydrophobic interaction (n=12) and polar hydrogen interaction (n=4). The molecular dynamic simulation revealed that the complex had an RMSF of 1.713 Å with a fluctuation of Rg value around 1.000 Å. The ADMET properties of ferulic acid suggested that the compound is an ideal drug candidate. In conclusion, this study suggested that ferulic acid, which can be isolated from palm oil waste, has the potential to interact with MCF-7 receptors.

Keywords: ADMET properties, cancer, ferulic acid, in silico, medicine

Introduction

Breast cancer is one of the most serious health problems, claiming the lives of 400,000 individuals with an average of 1,500,000 new cases globally each year [1]. In 2020, 2.3 million new cases and 685,000 deaths related to breast cancer were reported [2]. As the most common type of cancer in women, breast cancer incidence rate could reach 40 cases per 100,000 women. The trend of this disease is concerning, as a study in 2023 revealed that the mortality rate increased by 14% since 2018 [3]. Furthermore, a bibliometric analysis revealed that breast cancer is currently considered as a critical issue that significantly impacts women's health, particularly those living in Indonesia [4].

In general, the disease can be divided into benign and malignant types of breast cancer. Benign breast cancer is characterized by small, round, and soft lumps. Meanwhile, malignant breast cancer is characterized by asymmetrical shape, roughness, pain, and many other symptoms. The growth of breast cancer can spread between cells and other tissues and obstruct the body's metabolic functions [5]. Mammary glands, glandular ducts, and supportive breast tissue (fatty and connective tissue) can all harbor these cancers. Currently, the therapeutic treatment of this cancer is challenging. The definitive treatment is mostly performed by surgical removal of the affected tissue and chemotherapy, but they are constrained by a high cost [6]. Moreover, the cell cancer could develop resistance to the anticancer drugs, contributing to another difficulty in treating the disease [7]. Hence, the discovery of new drugs that can treat or prevent the growth of breast cancer cells is an urgent research topic.

On the other hand, Indonesia produced a substantial amount of palm oil in 2018, reaching up to 29.67 million tons, which has consequently resulted in a significant volume of agricultural solid waste [8-9]. Seeds and leaves of the oil palm, which constitute major solid waste, are rich in ferulic acid content, both in free form and bound to lignin or other biopolymers. [10]. Ferulic acid (4-hydroxy-3-methoxycinnamic acid) can be isolated from the palm oil solid waste and has been found to possess a wide range of pharmacological activities, including anti-inflammatory, anti-allergic, antiviral, anticancer, antioxidant, hepatoprotective, and antithrombotic properties [11]. The compound has been reported to exhibit various anti-cancer activities, from inducing apoptosis to autophagic cell death, depending on the cancer cell lines [12]. Modifications in the expression of procaspase-9, procaspase-8, procaspase-3, poly (ADP ribose) polymerase, Bcl-2, and Bax have been suggested to mediate the possible apoptotic activity of ferulic acid [13]. It was also found to have the ability to prevent the activation of the canonical Smad pathway and the kinase/Akt (protein kinase B) pathway that is controlled by extracellular signals that are not canonical. Therefore, the present study assessed the potential interaction of ferulic acid against the MCF-7 receptors to predict its activity as an anti-breast cancer agent.

In silico approaches were used in the present study to investigate the probable activities of ferulic acid in inhibiting the MCF-7 receptors. The aim of this study was to identify the drug targets of ferulic acid when acting as an anti-breast cancer agent. In silico approaches have been well employed in drug development because they may help identify ligand-receptor interactions, structural optimization, and synthesis [14]. Herein, in silico analysis of ferulic acid was conducted with several MCF-7 proteins as receptors to understand the basis of molecular interactions and binding affinity of these ligands with proteins. The receptors of MCF-7, specifically 1R5K, 2IOG, 4IV2, 4IW6, 5DUE, 5T92, and 5U2B, were selected based on the similarity of the Simplified Molecular Input Line Entry System (SMILES) of their respective native ligands. Performing in silico studies on proteins with close ligand similarity closely related ligands facilitates comparative analyses, which consequently provide better insights into binding affinities, structural variations, and potential cross-reactivity [15].

Methods

Study design

In silico approaches were employed in this study to elucidate the potential of ferulic acid in interacting with MCF-7-related receptors. First, the receptors were selected based on the similarity of their native ligand SMILES. Subsequently, the ferulic acid was assigned as the ligand

and computationally docked to the selected proteins. The best docking result was validated using molecular dynamic simulation. All computational simulations were performed on a Lenovo laptop equipped with an Intel Core i3-1115G4 Central Processing Unit operating at 3 GHz, running Windows 11 Ultimate 64-bit with 8 GB of random-access memory.

Selection of MCF-7 receptors

Initially, 50 non-mutated receptors related to MCF-7 were identified through a search on the RSCB Protein Data Bank (PDB). Following this, the receptors were clustered based on the native ligand's SMILES similarity. The clustering process was performed on the Datawarrior platform (https://openmolecules.org/datawarrior/), which supported the enumeration of combinatorial libraries and the generation of evolutionary models. Through this platform, the clustering was benefitted from the calculation of physicochemical properties and the prediction of the activity relationship [16]. The process identified a cluster comprised of 7 receptors with closely similar SMILES. The receptors were 1R5K, 2IOG, 4IV2, 4IW6, 5DUE, 5T92, and 5U2B, where their 3D structures are presented in **Figures 1A-1G**.

Preparation of ferulic acid structure

The ligand used in the computational simulation was ferulic acid ($C_{10}H_{10}O_4$; CAS number: 537-98-4). The 2D structure of ferulic acid was prepared by using ChemDraw Ver. 18 (PerkinElmer Informatics Inc., Shelton, Washington, USA). Subsequently, the 2D structure was converted into the 3D structure by using Chem3D Ver. 18 (PerkinElmer Informatics Inc., Shelton, Washington, USA). The generated 3D structure of ferulic acid is presented in **Figure 1H**.

Docking preparation

Docking preparation was carried out by utilizing Chimera 1.16 software. The seven receptors were aligned to standardize their 3D positions, ensuring that the coordinates (center x, y, and z) of their native ligands were consistent across all receptors. A grid box coordinate of x: 16.81, y: 7.88, and z: 14.78 was obtained and used for the docking with ferulic acid. The receptor was further prepared by the addition of hydrogen (addH) and partial atomic charge using the Gasteiger method. As for the ligand preparation, its SMILES was inputted to Balloon 1.8.2 software to generate the 3D structure in .sdf format. Open Babel software was subsequently utilized to optimize the atomic positions and reduce the molecular potential energy.

Molecular docking

Each receptor and its native ligand were respectively converted into a .pdb file for redocking protocol using Vina 1.2.5 docking software. The redocking with the native ligand was performed to compute the root mean square deviation (RMSD). We used RMSD<2 Å as the cut-off for validating the grid box coordinate. The three-dimensional simulated interactions between ferulic acid and the selected MCF-7 receptors were run on AutoDock Vina 1.2.5, following the suggestion from a previous study [17].

Molecular dynamics simulation

In order to determine the stability of the molecular complex, the docking results were validated using molecular dynamics simulations on CABS-flex 2.0 (https://biocomp.chem.uw.edu.pl/CABSflex2/index). The ligand-protein complex which tested in the simulation was selected based on the RMSD value as the stability indicator. The parameters of molecular dynamic simulation included the protein rigidity, restraints, number of cycles, C-alpha restraints weight, side-chain restraints weight, temperature range, trajectory, and random number generator seed. The setting of these parameters followed the protocols reported previously [18-19].

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions

The SMILES of ferulic acid was used to predict the ADMET properties on the pkCSM platform (http://biosig.unimelb.edu.au/pkcsm/), as suggested by a previous study [20]. Upon inserting the SMILES code and running the prediction, data on the pharmacokinetic and toxicological of the ferulic acids were collected. The prediction was run based on the pkCSM theory [21].
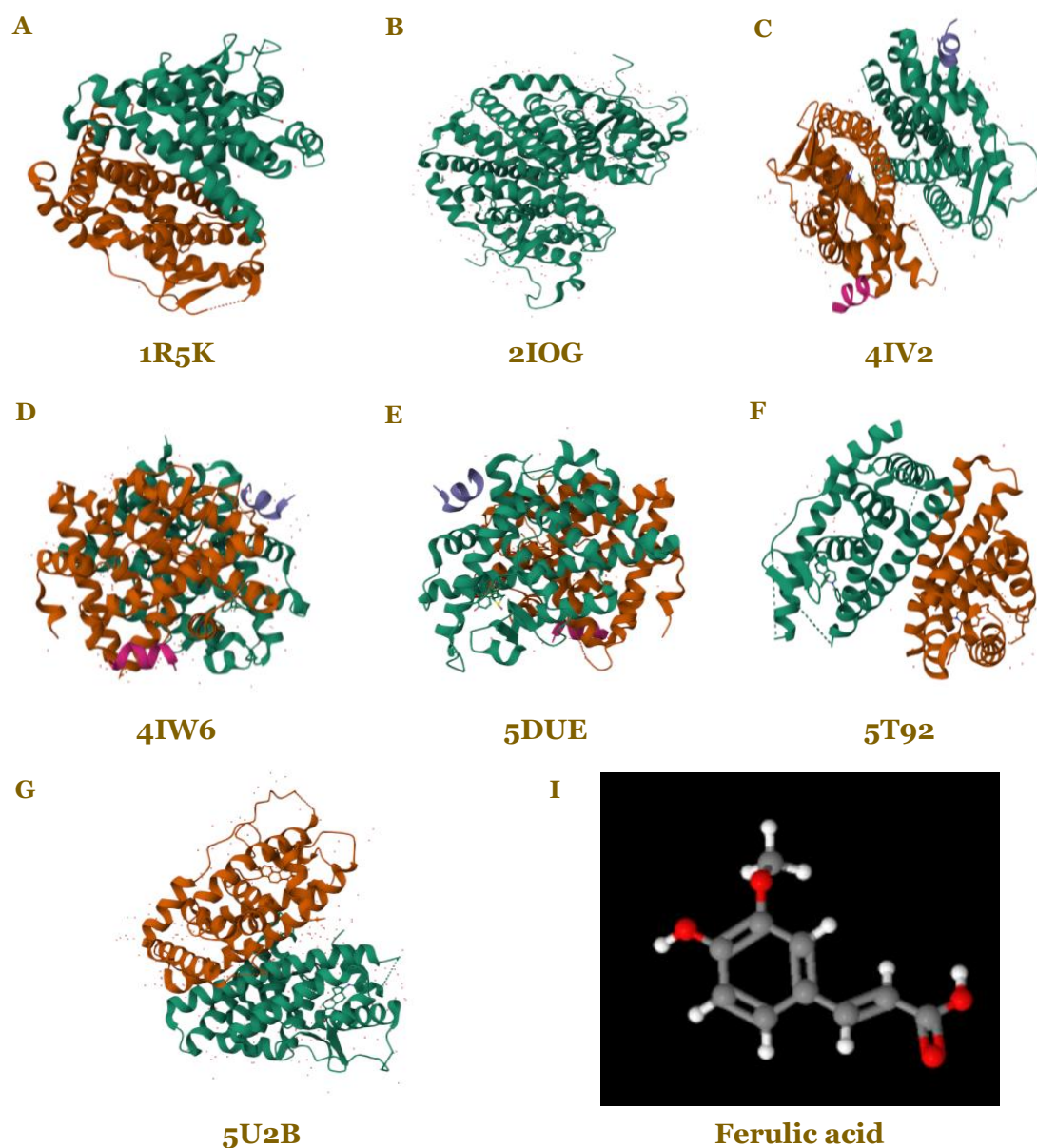
Figure 1. Three-dimensional structures of the MCF-7 receptors (A-G) and ferulic acid (I).

Results

Interaction between ferulic acid and MCF-7 receptors

Parameters calculated from the redocking with the native ligand and the molecular docking with ferulic acid are presented in **Table 1**. RMSD calculated at the best resolution ranged from 0.64 Å (2IOG) to 1.79 Å (4IV2). The highest involvement of polar hydrogen interaction (n=10) was observed in the interaction between ferulic acid and 4IW6. However, the affinity energy of the interaction was merely -6.21 kcal/mol. The best binding affinity (-6.96 kcal/mol) was found in the ferulic acid-2IOG complex. The 3D representation of the interaction between ferulic acid and 2IOG is presented in **Figure 2**. Since the ferulic acid-2IOG complex had the lowest RMSD and affinity energy, it was selected for molecular dynamic simulation.

Molecular dynamics results

The root mean square fluctuation (RMSF) plot was obtained from the molecular dynamics analysis of the ferulic acid-receptor 2IOG complex presented in **Figure 3**. The RMSF value for the complex was below 3 Å (1.713 Å), an indication of stable complex bonding. The molecular docking validation also revealed radius of gyration (Rg) was computed and presented in **Figure**

4. The Rg value of the ferulic acid-2IOG complex fluctuated near 1.000 Å and decreased on the minimum value of 0.100 Å, where only a few conformational changes were observed throughout the docking simulation.

Table 1. Result of redocking with the native ligand and docking with ferulic acid on selected MCF-7 receptors

Receptor	Resolution (Å)	RMSD (Å)	Affinity energy (kcal/mol)		Interaction	Amino acids
			Native ligand	Ferulic acid		
1R5K	2.70	1.70	-10.38	-6.36	HI	Leu525, Ile424, Ala350, Leu387
					PHI	Hoh700
2IOG	1.60	0.64	-12.23	-6.96	HI	Ala350, Cys530, Leu346, Leu354, Leu387, Leu391, Leu428, Phe425, Ile424, Trp383, Met421, Val418
					PHI	Glu353, Arg394, Gly521, Lys531
4IV2	2.14	1.79	-9.76	-6.16	HI	Leu346, Leu384, Leu387, Leu391, Ala350, Met421, Phe425, Ile424
					PHI	Arg394, Glu353, His524
4IW6	1.98	0.88	-10.10	-6.21	HI	Ala350 Ile424, Leu384, Leu387, Leu391, Leu525, Leu536, Leu540, Met388, Met421, Trp383
					PHI	Arg394, Glu353, Leu346, Leu349, Leu428, Phe425, His524, Met343, Thr347, Hoh701
5DUE	2.09	1.57	-10.94	-6.56	HI	Leu346, Leu387, Leu388, Leu391, Met388, Met421, Ala350
					PHI	Glu353, Glu419, Thr347, Gly521
5T92	2.22	1.77	-11.95	-6.44	HI	Leu387, Leu391, Leu525, Ala350, Met388, Met421, Ile424
					PHI	Glu353, Arg394, His524
5U2B	1.59	0.70	-11.21	-6.13	HI	Leu387, Leu391, Leu525, Met343, Met421, Ile424, Ala35
					PHI	Glu353, Arg394

HI: hydrophobic interaction; PHI: polar hydrogen interaction; RMSD: root mean square deviation
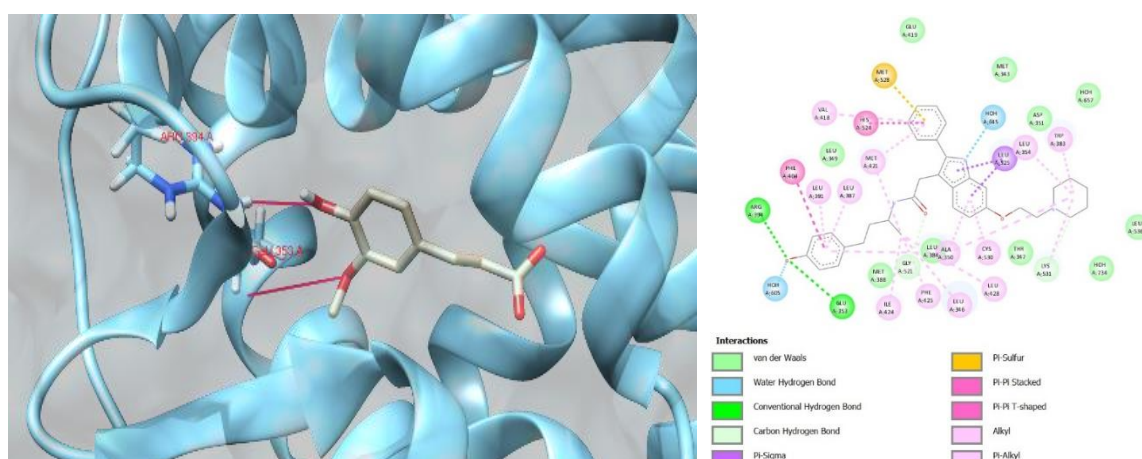

Figure 2. Three-dimensional interaction between ferulic acid and receptor 2IOG. The ligand-protein complex has the best binding affinity and root mean square deviation (RMSD) scores of -6.96 kcal/mol and 0.64 Å, respectively.
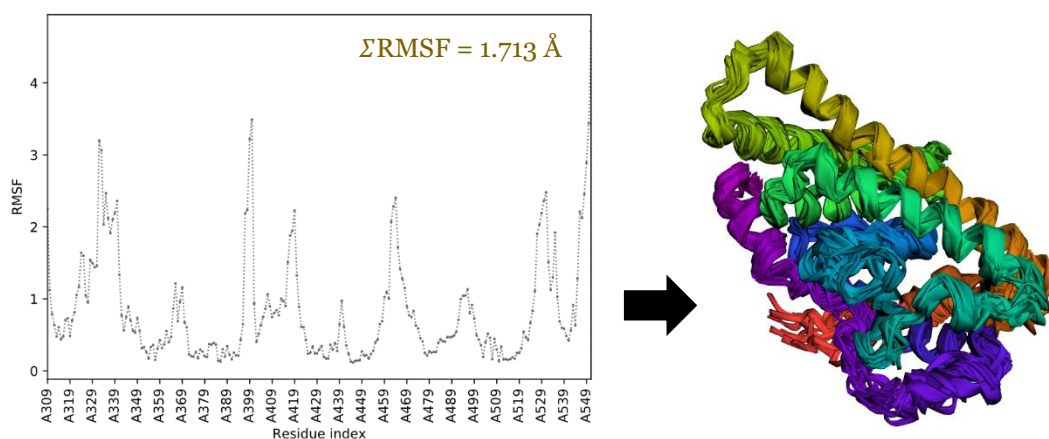
Figure 3. Root mean square fluctuation (RMSF) plot obtained from the molecular dynamic simulation of ferulic acid-receptor 2IOG complex.
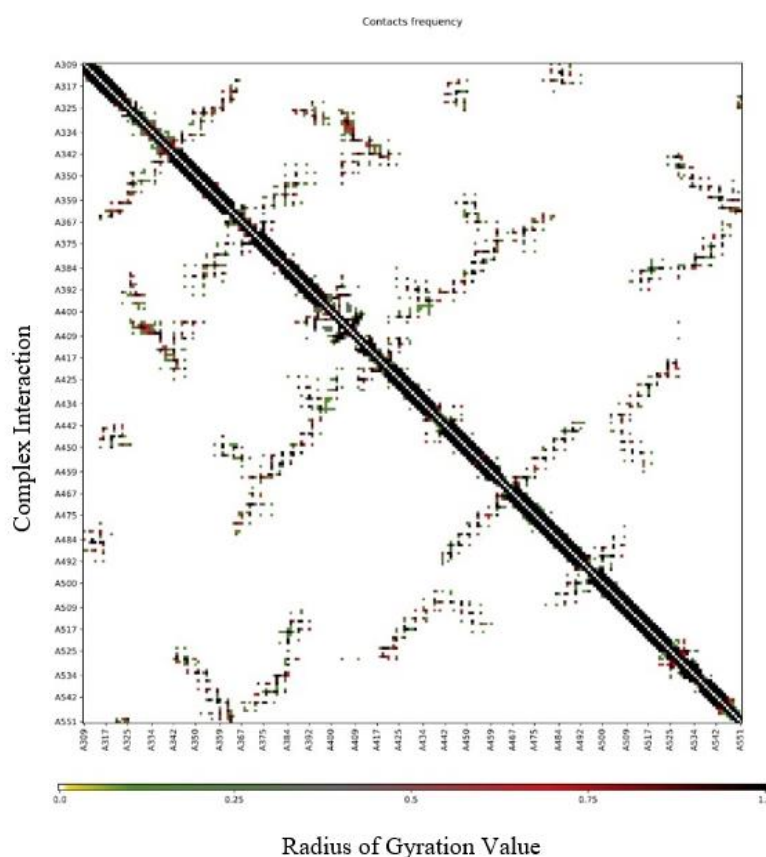

Figure 4. The radius of gyration value of ferulic acid-receptor 2IOG complex. The Σ radius of gyration (Rg) is equal to 1.000 Å.

ADMET properties analysis results

The ADMET properties of ferulic acid are presented in **Table 3**. In terms of absorption, the compound was predicted to have a water solubility of -2.917 logS and a $CaCO_2$ permeability of -0.047 logPapp, with a high human intestinal absorption rate of 94.87%. Regarding distribution, the volume of distribution at steady state in humans was predicted to be -1.132 logL/kg, where the blood-brain barrier permeability was found to be -0.253 cm/s. For the metabolism parameter, the compound was not a substrate for CYP2D6 or CYP3A4 enzymes. Excretion prediction showed that the compound was not a substrate for the renal organic cation transporter and had a total clearance rate of 0.655 log mL/min/kg. In terms of toxicity, the rat LD_{50} was predicted to be 2.325 mol/kg. The prediction also revealed that the compound was unlikely to exhibit toxicity based on the Ames test.

Table 3. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties prediction of ferulic acid

Parameters	ADMET properties	Value or remark
Absorption	Water solubility (logS)	-2.917
	$CaCO_2$ permeability (logPapp)	-0.047
	Human intestinal absorption (%)	94.871
Distribution	Volume of distribution at steady state (human) (logL/kg)	-1.132
	Blood-brain barrier permeability (cm/s)	-0.253
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	No
Excretion	Renal organic cation transporter	No
	Total clearance (log mL/min/kg)	0.655
Toxicity	Rat LD_{50} (mol/kg)	2.325
	Ames toxicity	No

Discussion

In the present study, the docking experiment suggested that ferulic acid has the potential to interact with MCF-7 receptors, thus impairing the growth of breast cancer. Ferulic acids form the interaction with the receptors through hydrogen and hydrophobic bonds. The validity of our docking results was supported by the RMSD value of less than 2 Å, as suggested by previous studies [22-23]. Receptor 2IOG particularly had the lowest RMSD score of 0.64 Å with a redocking score of -10.38 kcal/mol. With an RSMF value less than 3 Å, this interaction is not only shown to be strong but also stable and less likely to be deviated in the real experiment. Similarly, the strong and stable interaction was corroborated by the Rg value that fluctuated near 1.000 Å and decreased on the minimum value of 0.1 Å.

Further analysis of the ADMET properties of ferulic acid described the probable biological activities of the compound. In comparison with previous studies, the water solubility and $CaCO_2$ permeability of ferulic acid could be categorized as low [24-25]. Moreover, ferulic acid was found to have a low volume of distribution at steady state (<-0.15 logL/kg), suggesting that the compound would be difficult to spread across tissue [26]. In accordance with a previous study, the low blood-brain barrier permeability suggested that ferulic acid would not affect the human brain. We also noted that the ferulic acid was predicted as a non-substrate for CYP2D6 and CYP3A4 enzymes. As the two enzymes did not metabolize the compound, the interaction with the drug target, including the MCF-7 receptors, was likely to occur [27-28]. Our finding also suggested that ferulic acid was not a substrate for renal organic cation transporter. This condition might indicate that ferulic acid might have a longer half-life and prolonged therapeutic effects [29-30]. It is noteworthy that, apart from being retained in the body, the compound was predicted to be non-toxic according to the Ames toxicity test, particularly in causing angiogenesis to the cancer cell.

A previous docking experiment uncovered the potential of ferulic acid derivatives on the P2Y12 receptor. Ferulic acid expressed non-toxic activity against normal cells and its penetration in the blood-brain barrier was found to be moderate. Nonetheless, the penetration ability of this compound was found to be ineffective in inhibiting the CYP2D6 and CYP3A4 enzymes [26]. Another study found that ferulic acid and its derivatives could act as antagonists for angiogenesis. The target of the receptors was found to be fibroblast growth factor receptor-1, a key angiogenesis receptor in the cancer growth pathway. Modifying ferulic acid by replacing the phenolic moiety with the ester was revealed to increase its bioactivity and ADMET profile [31-35].

Our findings contributed to the understanding of ferulic acid's potential as an anti-breast cancer agent. However, some limitations in this study are worthy of consideration, including the predictive nature of the data generated in this study. Moreover, the prediction excludes the consideration of the physiological and biological factors affecting the ligand-protein interaction. Further research approaches, such as in vivo and in vitro, are needed to support the findings in the present in silico study.

Conclusion

Ferulic acid, an abundantly available bioactive compound in palm oil waste, may form interactions with MCF-7 receptors, particularly receptor 2IOG. Further, the compound had ideal

pharmacokinetic activity as a drug candidate with low mutagenic and toxicity activity. Our findings recommend confirming the ferulic acid's anti-breast cancer potential through in vivo and in vitro analysis.

Ethics approval

None.

Acknowledgments

We thank Jalan Tengah, Indonesia (www.jalantengah.site) for editing the manuscript.

Competing interests

All the authors declare that there are no conflicts of interest in any capacity, including competing or financial.

Funding

None.

Underlying data

Underlying data are available upon request from the corresponding author.

How to cite

Herdiansyah MA, Rizaldy R, Alifiansyah MRT, *et al*. Molecular interaction analysis of ferulic acid (4-hydroxy-3-methoxycinnamic acid) as main bioactive compound from palm oil waste against MCF-7 receptors: An in silico study. Narra J 2024; 4 (2): e775 - http://doi.org/10.52225/narra.v4i2.775.

References

1. Adamowicz K, Baczkowska-Waliszewska Z. Quality of life during chemotherapy, hormonotherapy or antiHER2 therapy of patients with advanced, metastatic breast cancer in clinical practice. Health Qual Life Outcomes 2020;18(1):134.

2. Arnold M, Morgan E, Rumgay H, *et al*. Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast 2022;66:15-23.

3. Breast Cancer Research Foundation. Breast Cancer Statistic and Resources. New York: Breast Cancer Research Foundation; 2023.

4. Iqhrammullah M, Refin RY, Rasmi RI, *et al*. Cancer in Indonesia: A bibliometric surveillance. Narra X 2023;1(2):e86.

5. Stender JD, Nwachukwu JC, Kastrati I, *et al*. Structural and molecular mechanism of cytokine-mediated endocrine resistance in human breast cancer cells. Mol Cell 2017;65(1):1122-1135.

6. Feng Y, Spezia M L, Huang S, *et al*. Breast cancer development and progression: Risk factors, cancer stem cells, signalling pathways, genomics, and molecular pathogenesis. Genes Dis 2018;5(2):77-106.

7. Paduraru DN, Alexandra B, Ion D, *et al*. Latest news and trends in what concerns the risk factors of endometrial cancer. Rom Biotechnol Lett 2018;23(5):14056-14066.

8. Koplitz SN, Mickley LJ, Marlier ME, *et al*. Public health impacts of the severe haze in equatorial Asia in September-October 2015: Demonstration of a new framework for informing fire management strategies to reduce downwind smoke exposure. Environ Res Lett 2016;11:094023.

9. Sari DW, Hidayat FN, Abdul I. Efficiency of land use in smallholder palm oil plantations in Indonesia: A stochastic frontier approach. For Soc 2021;5(1):75-89.

10. Sundalian M, Larissa D, Suprijana O. Contents and utilization of palm oil fruit waste. Biointerface Res Appl Chem 2021;11(3):10148-10160.

11. Zhai Y, Wang T, Fu Y, *et al*. Ferulic acid: A review of pharmacology, toxicology, and therapeutic effects on pulmonary diseases. Int J Mol Sci 2023;24(9):8011.

12. Gupta A, Singh AK, Loka M, *et al*. Ferulic acid-mediated modulation of apoptotic signaling pathways in cancer. Adv Protein Chem Struct Biol 2021;125:215-257.

13. Chang DW, Xing Z, Capacio VL, et al. Interdimer processing mechanism of procaspase-8 activation. EMBO J 2003;22(16):4132-4142.

14. Arman M, Alam S, Maruf RA, et al. Molecular modeling of some commercially available antiviral drugs and their derivatives against SARS-CoV-2 infection. Narra J 2024;4(1):e319.

15. Tassakka AC, Iskandar IW, Juniyazaki AB, et al. Green algae Caulerpa racemosa compounds as antiviral candidates for SARS-CoV-2: In silico study. Narra J 2023;3(2):e179.

16. Sander T, Freyss J, von Korff M, et al. DataWarrior: An open-source program for chemistry aware data visualization and analysis. J Chem Inf Model 2015;55(2):460-473.

17. Eberhardt J, Santos-Martins D, Tillack AF, et al. AutoDock Vina 1.2.0: New docking methods, expanded force field, and Python bindings. J Chem Inf Model 2021;61(8):3891-3898.

18. Shivanika C, Kumar D, Ragunathan V, et al. Molecular docking, validation, dynamics simulations, and pharmacokinetic prediction of natural compounds against the SARS-CoV-2 main-protease. J Biomol Struct Dyn 2022;40(2):585-611.

19. Anandan S, Gowtham HG, Shivakumara CS, et al. Integrated approach for studying bioactive compounds from Cladosporium spp. against estrogen receptor alpha as breast cancer drug target. Sci Rep 2022;12(1):22446.

20. Pires DE, Blundell TL, Ascher DB. pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem 2015;58(9):4066-4072.

21. Jia CY, Li JY, Hao GF, et al. A drug-likeness toolbox facilitates ADMET study in drug discovery. Drug Discov Today 2020;25(1):248-258.

22. Ekowati J, Diyah NW, Nofianti KA, et al. Molecular docking of ferulic acid derivatives on P2Y12 receptor and their ADMET prediction. J Math Fund Sci 2018;50(2):203-219.

23. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: A review. Biophys Rev 2017;9(2):91-102.

24. Gleeson MP. Generation of a set of simple, interpretable ADMET rules of thumb. J Med Chem 2008;51(4):817-834.

25. Paul A. Drug absorption and bioavailability. In: Raj G, Raveendran R, editors. Introduction to basics of pharmacology and toxicology. Singapore: Springer; 2019.

26. Jeffrey P, Summerfield S. Assessment of the blood-brain barrier in CNS drug discovery. Neurobiol Dis 2010;37(1):33-37.

27. Hadni H, Elhallaouia M. In silico design of EGFRL858R/T790M/C797S inhibitors via 3D-QSAR, molecular docking, ADMET properties and molecular dynamics simulations. Heliyon 2022;8(11):e11537.

28. Rizzieri D, Paul B, Kang Y. Metabolic alterations and the potential for targeting metabolic pathways in the treatment of multiple myeloma. J Cancer Metastasis Treat 2019;5:26.

29. Garza AZ, Park SB, Kocz R. Drug Elimination. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.

30. Wilde M, Pichini S, Pacifici R, et al. Metabolic pathways and potencies of new fentanyl analogs. Front Pharmacol 2019;10:238.

31. Ramadhan DR, Ekowati J, Pebrianti D, et al. Docking study of ferulic acid derivatives on FGFR1, ADME prediction, and QSPR analysis. Pharm Educ 2024;24(3):178-184.

32. Herdiansyah MA, Ansori ANM, Kharisma VD, et al. In silico study of cladosporol and its acyl derivatives as anti-breast cancer against alpha-estrogen receptor. Biosaintifika 2024;16(1):142-154.

33. Zainul R, Kharisma VD, Ciuputri P, et al. Antiretroviral activity from elderberry (Sambucus nigra L.) flowers against HIV-2 infection via reverse transcriptase inhibition: A viroinformatics study. Healthc Low-resource Settings 2024;1(1):1-12.

34. Alifiansyah MRT, Herdiansyah MA, Pratiwi RC, et al. QSAR of acyl alizarin red biocompound derivatives of Rubia tinctorum roots and its ADMET properties as anti-breast cancer candidates against MMP-9 protein receptor: In silico study. Food Syst 2024;7(2):312-320.

35. Krihariyani D, Haryanto E, Sasongkowati R. In silico analysis of antiviral activity and pharmacokinetic prediction of brazilein sappan wood (Caesalpinia sappan L.) against SARS-CoV-2 spike glycoproteins. Indones J Med Lab Sci Technol 2021;3(1):26-37.