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Prediction Activity Pharmacology and Molecular Docking of Secondary Metabolite Compounds of Tamarind Leaves (*Tamarindus indica*) as Anticancer

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ABSTRACT

Introduction*: Cancer remains one of the leading causes of morbidity and mortality worldwide, with incidence and death rates increasing annually. One of the most effective therapeutic targets for cancer is the Epidermal Growth Factor Receptor (EGFR). However, the use of synthetic EGFR inhibitors is often associated with significant side effects.* ***Aims****: This study aims to evaluate the potential of compounds derived from Tamarindus indica (tamarind) leaves as anticancer agents through an in silico approach, including pharmacological activity prediction (PASS) and molecular docking against the EGFR receptor.* ***Methods****: Pharmacological activities were predicted using the Way2Drug webtool, while molecular docking analysis was performed using Molegro Virtual Docker (MVD).* ***Result****: The PASS prediction results indicated that the compounds in Tamarindus indica leaves possess a broad spectrum of anticancer activities. Docking analysis revealed that isovitexin exhibited the lowest rerank score among the test compounds and controls (erlotinib and the native ligand), indicating stronger binding affinity to EGFR.* ***Conclusion****: These findings support the potential of tamarind leaves, particularly isovitexin, as a promising computationally-predicted anticancer therapeutic candidate.*

KEYWORDS*: Tamarindus indica, EGFR, isovitexin, PASS prediction, molecular docking, anticancer*

INTRODUCTION

Cancer represents one of the major burdens in terms of social, public health, and economic aspects in the 21st century. Global data show that in 2022, cancer caused approximately 9.7 million deaths and recorded more than 20 million new cases, an increase from figures reported in 2020 (Lin et al., 2021; Aayishamma et al., 2024). The burden of cancer-related deaths is projected to continue rising substantially in the coming decades. By 2025, cancer mortality is expected to reach 11.5 million, and by 2035, the number may rise to 14.6 million. Among men, the most common cancers are lung, colorectal, prostate, liver, and stomach cancer, while in women, breast, lung, cervical, colorectal, and thyroid cancers dominate (Aayishamma et al., 2024).

Cancer is characterized by uncontrolled

abnormal cell growth, with the potential to invade and spread to surrounding tissues and organs. Although various treatment modalities are available, chemotherapy remains one of the main pillars of cancer therapy. However, chemotherapy has several limitations, such as limited efficacy, low selectivity toward cancer cells, genetic toxicity, and drug resistance. In addition, damage to normal cells and organ toxicity due to chemotherapy can significantly reduce the quality of life for cancer patients (Tang et al., 2017). Without effective intervention, cancer-related deaths could reach 16.2 million by 2040 (Schüz & Espina, 2021).

One of the molecular targets proven effective in cancer therapy is the Epidermal Growth Factor Receptor (EGFR), a founding member of the growth factor receptor family with intrinsic tyrosine kinase activity. EGFR has become one of the most successful pharmacological targets in cancer therapy (Yarden & Pines, 2012; Uribe et al., 2021). Inhibition of EGFR tyrosine kinase activity is typically achieved using small molecules that bind to and inhibit the enzyme. To date, more than 10 EGFR inhibitors have been approved by the U.S. Food and Drug Administration (FDA) in the past two decades, including Erlotinib, Lazertinib, Gefitinib, Imatinib, and Lapatinib, which are generally based on quinazoline derivatives (Al-Anazi et al., 2018; Khalilullah et al., 2022; Shi et al., 2022). Although effective, the use of quinazoline-based inhibitors is still limited by the occurrence of side effects such as skin rashes, diarrhea, nausea, vomiting, and bleeding, thus necessitating the development of new anticancer agents with lower toxicity (Al-Anazi et al., 2022).

Tamarindus indica L., commonly known as tamarind, belongs to the Fabaceae family, subfamily Caesalpinioideae, and is a multifunctional tropical plant widely used across Asia, including in Indonesia, India, Thailand, Sri Lanka, and Bangladesh (De Caluwe et al., 2010). Almost all parts of this plant have potential applications, both as food and traditional medicine. Various constituents such as carbohydrates, proteins, fats, tannins, essential amino acids, vitamins, minerals, and phytochemicals have been identified in this plant. Furthermore, numerous pharmacological activities have been reported, including antidiabetic, antioxidant, anticancer, antihepatotoxic, anti-inflammatory, and antimutagenic effects (Ferrara, 2019; Radha & Kusum, 2024).

This study aims to evaluate the anticancer potential of compounds present in *Tamarindus indica* leaves through an in silico approach, focusing on their ability to inhibit EGFR activity as a key molecular target in cancer therapy.

MATERIAL AND METHODS

Material

This in silico study utilized the Epidermal Growth Factor Receptor (EGFR) as the target protein, obtained from the Protein Data Bank (https://www.rcsb.org) with PDB ID: 1M17. The active compounds contained in *Tamarindus indica* (tamarind) leaves have been identified in previous research by Sholikhah et al. (2024), and these compounds were used as test ligands in this study. The compounds in question include Isovitexin, Isovitexin 2'-O-Arabinoside, Orientin, (-)-Epicatechin, and Hexadecanamide (Sholikhah et al., 2024). As comparison ligands, the 3D structures of the native ligand and Erlotinib were used (Putra et al., 2023).

Tools

The equipment used in this study included a computer with the following specifications: Asus brand, Windows 11 64-bit operating system, AMD Ryzen™ 7 7435HS 3.1GHz processor, 8 GB RAM, and 500 GB SSD storage. The software employed included Molegro Virtual Docker (MVD) version 5, ChemOffice Professional 22.0, Chem3D 22.0, and the Protein Data Bank (PDB) for protein structure data.

Screening Activity Pharmacology

The simplified molecular-input line-entry system (SMILES) codes of each compound were obtained through the PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/). These codes were then inputted into the Way2Drug PASS Online webtool (https://www.way2drug.com/passonline/predict.php) to computationally predict pharmacological activity (Andhiarto et al., 2024; Muslikh & Prasetyawan, 2024). Analysis was performed using keywords related to "cancer" to screen for potential anticancer activity (Hartati et al., 2024).

Preparation Protein Structure

The crystal structure of the Epidermal Growth Factor Receptor (EGFR) protein was retrieved from the Protein Data Bank (https://www.rcsb.org) with PDB ID 1M17 (Gowtham et al., 2024; Suhail et al., 2025).

Preparation Ligand Structure

All compounds in 2D structure were obtained from PubChem and then prepared by removing water molecules and minimizing energy using ChemDraw version 22.0 (Poy & Tohidfar, 2024). The structures were converted into 3D using Chem3D version 22.0. Geometry optimization and identification of the most stable conformation were performed using the MMFF94 force field method (Álvarez et al., 2023). The optimized files were saved in SDF format for use in molecular docking analysis (Pratama et al., 2023).

Docking and Analysis Proces Amino Acid Interaction

Moleculer docking and amino acid residue interaction analysis were caried out using

MVD. The ligand binding site was defined by selecting the active cavity in the target protein structure (Liao et al., 2022). The active cavity used was located at spatial coordinates X: 21.58; Y: 0.40; and Z: 52.48, with a radius of 10 Å. Parameters measured during docking included energy values such as MolDock Score, Rerank Score, Hbond, and RMSD. Among these, the Rerank Score is often used to assess the binding strength between drug and receptor (Yuliani et al., 2024)

RESULTS AND DISCUSSION

The results of the predicted biological activity of compounds from *Tamarindus indica* leaves are presented in Table 1. The table shows that these compounds exhibit potential anticancer activity against various types of cancer, including breast, cervical, brain, prostate, and thyroid cancers. These predictions are based on the Pa (probability to be active) values, which indicate the likelihood that a compound belongs to the subclass of active compounds based on chemical structures commonly found in the PASS active compound database (Khaiitova, 2023; Muslikh & Prasetyawan, 2024). In contrast, the Pi (probability to be inactive) values reflect the likelihood that the compound is inactive, based on structural similarity with compounds classified as inactive in the PASS system (Muslikh & Prasetyawan, 2024).

Prediction of activity spectra for substances (PASS) is a computer-based software tool that can predict the biological activity of organic molecules resembling drug-like compounds. PASS enables simultaneous prediction of various types of biological activities based on a compound's chemical structure through in silico analysis, prior to chemical synthesis or experimental biological testing, making it an efficient tool for early-stage drug discovery (Muslikh, 2024).

The molecular docking method was used to evaluate the interaction between ligands and the target protein, in this case, the Epidermal Growth Factor Receptor (EGFR). This technique calculates binding energies using molecular mechanics and includes stages such as virtual screening, prediction of binding poses, interaction analysis, and evaluation of binding affinity and ligand-protein complex conformation (Prieto-Martinez et al., 2018; Mursal et al., 2024) Ligands with lower binding free energy are generally considered to have better binding affinity and are regarded as potential therapeutic candidates (Lesmana et al., 2022).

In this study, molecular docking was performed using the software MVD to determine interaction energies between proteins and ligands in a fully integrated computational package (Ferreira & Jr, 2019; Suryanto et al., 2025). This software has an

Table 1. Predictions activity anticancer compound of *Tamarindus indica* leaves

Compound	Pa	Pi	Activities
Isovitexin	0.380	0.035	Antineoplastic (breast cancer)
	0.325	0.015	Antineoplastic (cervical cancer)
	0.323	0.020	Antineoplastic (small cell lung cancer)
	0.318	0.047	Antineoplastic (pancreatic cancer)
	0.303	0.039	Antineoplastic (lung cancer)
	0.274	0.038	Antineoplastic (brain cancer)
	0.248	0.020	Antineoplastic (renal cancer)
	0.264	0.044	Antineoplastic (colorectal cancer)
	0.235	0.020	Antineoplastic (bladder cancer)
	0.251	0.043	Antineoplastic (colon cancer)
	0.201	0.024	Antineoplastic (gastric cancer)
	0.156	0.028	Antineoplastic (uterine cancer)
	0.165	0.051	Antineoplastic (ovarian cancer)
	0.189	0.080	Prostate cancer treatment
	0.172	0.069	Antineoplastic (thyroid cancer)
Isovitexin 2'-O-Arabinoside	0.441	0.026	Antineoplastic (breast cancer)
	0.413	0.021	Antineoplastic (lung cancer)
	0.350	0.013	Antineoplastic (cervical cancer)
	0.333	0.017	Antineoplastic (small cell lung cancer)
	0.335	0.038	Antineoplastic (pancreatic cancer)
	0.278	0.028	Antineoplastic (liver cancer)
	0.255	0.019	Antineoplastic (renal cancer)
	0.236	0.051	Antineoplastic (colorectal cancer)
	0.242	0.065	Antineoplastic (brain cancer)
	0.225	0.049	Antineoplastic (colon cancer)
	0.198	0.038	Antineoplastic (ovarian cancer)
	0.170	0.019	Antineoplastic (uterine cancer)
	0.177	0.033	Antineoplastic (gastric cancer)
	0.178	0.074	Antineoplastic (bladder cancer)
	0.174	0.093	Prostate cancer treatment
	0.155	0.149	Antineoplastic (non-small cell lung cancer)
Orientin	0.428	0.027	Antineoplastic (breast cancer)
	0.332	0.015	Antineoplastic (cervical cancer)
	0.320	0.020	Antineoplastic (small cell lung cancer)
	0.334	0.038	Antineoplastic (pancreatic cancer)
	0.326	0.035	Antineoplastic (lung cancer)
	0.279	0.040	Antineoplastic (colorectal cancer)
	0.265	0.039	Antineoplastic (colon cancer)
	0.266	0.044	Antineoplastic (brain cancer)
	0.240	0.023	Antineoplastic (renal cancer)
	0.208	0.022	Antineoplastic (gastric cancer)
	0.235	0.061	Prostate cancer treatment
	0.210	0.036	Antineoplastic (bladder cancer)
	0.177	0.046	Antineoplastic (ovarian cancer)
	0.180	0.055	Antineoplastic (thyroid cancer)
	0.142	0.042	Antineoplastic (uterine cancer)
	0.180	0.106	Antineoplastic (non-small cell lung cancer)
	0.082	0.033	Breast cancer-resistant protein inhibitor

Table 1. Predictions activity anticancer compound of *Tamarindus indica* leaves

Compound	Pa	Pi	Activities
Orientin	0.428	0.027	Antineoplastic (breast cancer)
	0.332	0.015	Antineoplastic (cervical cancer)
	0.320	0.020	Antineoplastic (small cell lung cancer)
	0.334	0.038	Antineoplastic (pancreatic cancer)
	0.326	0.035	Antineoplastic (lung cancer)
	0.279	0.040	Antineoplastic (colorectal cancer)
	0.265	0.039	Antineoplastic (colon cancer)
	0.266	0.044	Antineoplastic (brain cancer)
	0.240	0.023	Antineoplastic (renal cancer)
	0.208	0.022	Antineoplastic (gastric cancer)
	0.235	0.061	Prostate cancer treatment
	0.210	0.036	Antineoplastic (bladder cancer)
	0.177	0.046	Antineoplastic (ovarian cancer)
	0.180	0.055	Antineoplastic (thyroid cancer)
	0.142	0.042	Antineoplastic (uterine cancer)
	0.180	0.106	Antineoplastic (non-small cell lung cancer)
	0.082	0.033	Breast cancer-resistant protein inhibitor
(-)-Epicatechin	0.486	0.020	Antineoplastic (breast cancer)
	0.426	0.018	Prostate cancer treatment
	0.278	0.048	Antineoplastic (small cell lung cancer)
	0.282	0.073	Antineoplastic (pancreatic cancer)
	0.198	0.011	Antineoplastic (uterine cancer)
	0.182	0.056	Antineoplastic (renal cancer)
	0.193	0.073	Antineoplastic (lung cancer)
	0.263	0.153	Cancer associated disorders treatment
	0.156	0.056	Antineoplastic (ovarian cancer)
	0.164	0.088	Antineoplastic (thyroid cancer)
	0.092	0.024	Breast cancer-resistant protein inhibitor
	0.202	0.148	Antineoplastic (bone cancer)
	0.168	0.126	Antineoplastic (non-small cell lung cancer)
	0.168	0.126	Antineoplastic (non-small cell lung cancer)
Hexadecanamide	0.390	0.017	Cancer associated disorders treatment
	0.243	0.019	Cancer procoagulant inhibitor
	0.214	0.038	Antineoplastic (endocrine cancer)
	0.222	0.087	Antineoplastic (bone cancer)
	0.202	0.083	Antineoplastic (liver cancer)
	0.153	0.125	Antineoplastic (bladder cancer)

advantage in accurately predicting ligand binding modes, with an accuracy rate of 87.0%, which is higher than other docking software such as Glide (81.8%), GOLD (78.2%), Surflex (75.3%), and FlexX2 (57.9%) (Kaushik et al., 2014; Maurya et al., 2023). In this study, the root mean square deviation (RMSD) parameter and visual analysis were used to validate the reliability of the molecular docking method. Validation was performed through a redocking process, where the ligand was repositioned into the

Table 2. Results of molecular docking of compounds leaf Tamarind against EGFR

Ligand	Rerank Score	MolDock Score	HBond
Isovitexin	-110.215	-117.202	-14.7724
AQ4_999 [A]	-107.073	-128.051	-2.5
Isovitexin 2'-O-Arabinoside	-103.295	-107.542	-10.2754
Erlotinib	-99.6135	-121.683	-2.5
Orientin	-93.1031	-101.647	-95.3398
(-)-Epicatechin	-72.7134	-78.1686	-7.62602
Hexadecanamide	-67.3853	-81.2804	-1.78668

same active site of the receptor from its original location in the crystal structure (Figure 1) . An RMSD value below 2.0 Å typically indicates high prediction accuracy (Osman et al., 2020). In this study, the RMSD value obtained was 1.3198 Å, indicating good agreement between the docking result and the reference structure, thereby supporting the validity of the method used (Lesmana et al., 2022; Gondokesumo et al., 2024).

In addition to RMSD, the primary parameter analyzed was the rerank score, which represents the total binding energy required to form a ligand-receptor complex. A lower or more negative rerank score indicates a more stable interaction between the ligand and the receptor (Yuliani et al., 2024). Therefore, compounds with lower rerank scores are considered to have better binding affinity and higher potential as therapeutic candidates (Ibrahim et al., 2020; Poy & Tohidffar, 2024).

Based on Table 2, the compound isovitexin showed the lowest rerank score compared to the other test compounds, including the native ligand (AQ4_999 [A]) and Erlotinib, a commonly used tyrosine kinase inhibitor in cancer therapy. The lower rerank score indicates that isovitexin has a higher binding affinity toward the EGFR receptor, making it a promising candidate for anticancer activity (Ibrahim et al., 2020; Poy & Tohidffar, 2024).

This finding is further supported by the analysis of amino acid residue interactions at the EGFR active site, as shown in Figure 2 and Table 3. Isovitexin demonstrated a significant similarity in interaction patterns with the native ligand, both in terms of the interacting residues and their positions. This indicates that isovitexin can mimic the natural ligand binding mechanism to the receptor, thereby supporting its potential biological activity as an EGFR inhibitor.

EGFR is a transmembrane receptor of the tyrosine kinase family that plays a critical role in transducing signals from the extracellular environment into the cell. EGFR

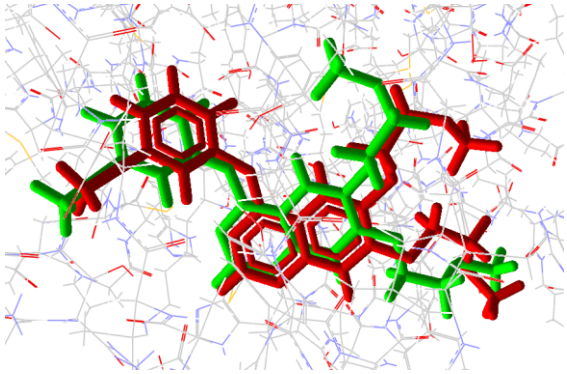

Figure 1. Results of overlay of ligand (red) and native ligand (green)

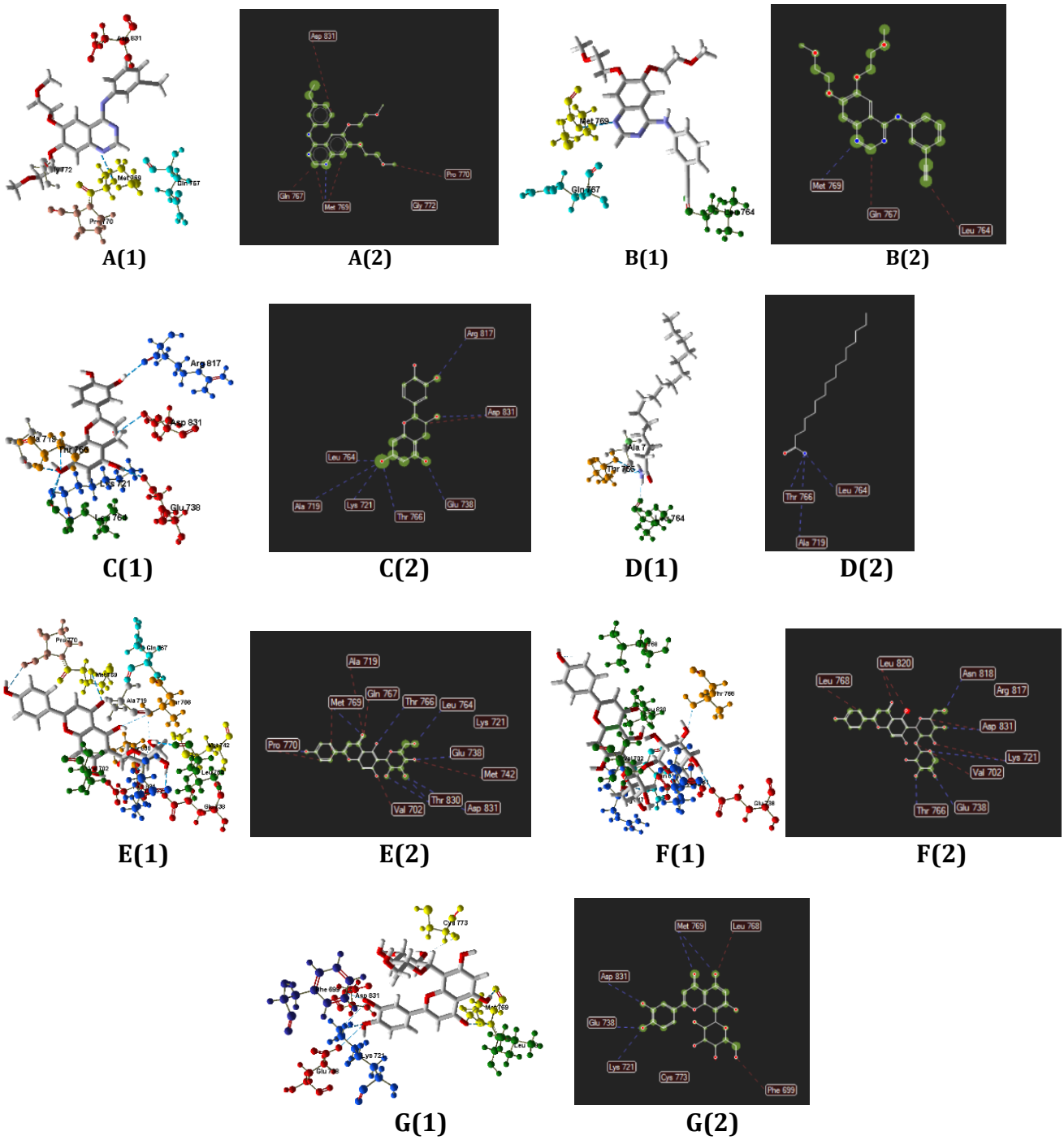

Figure 2. Visualization interaction amino acids. A. AQ4_999 [A]; B. Erlotinib; C. (-)-Epicatechin; D. Hexadecanamide; E. Isovitexin; F. Isovitexin 2'-O-Arabinoside; G. Orientin. (1) 3D Structure; (2) 2D structures.

Table 3. Interactions bond residue amino acid compound leaf Tamarind against EGFR

Compound	Hydrogen Bonds	Steric Bonds
AQ4_999 [A]	Met769	Asp831, Gln767, Met769, Gly772, Pro770
Erlotinib	**Met769**	**Met769**, **Gln767**, Leu764
(-)-Epicatechin	Ala719, Lys721, Glu738, **Asp831**, Arg817	Leu764, Thr766, Ala719, Lys721, Glu738, **Asp831**, Arg817
Hexadecanamide	Thr766, Ala719, Leu764	Thr766, Ala719, Leu764
Isovitexin	**Pro770**, **Met769**, Thr766, Leu764, Glu738, **Asp831**, Thr830	**Pro770**, Ala719, **Gln767**, Thr766, Lys721, Leu764, Met742, Glu738, Thr830, **Asp831**, Val702, **Met769**
Isovitexin 2'-O-Arabinoside	Asn818, **Asp831**, Lys721, Glu738, Thr766	Leu768, Leu820, **Asp831**, Asn818, Arg817, Val702, Lys721, Glu738, Thr766
Orientin	**Met769**, **Asp831**, Glu738, Lys721	**Met769**, Leu768, Glu738, **Asp831**, Lys721, Cys773, Phe699

*Bold text to signify similar with native ligand (AQ4_999[A])

activation can occur via ligand binding, overexpression, or mutation, and is known to play a vital role in tumorigenesis and progression of various cancers (Subramaniyan et al., 2022). Therefore, EGFR is an important target in cancer therapy development, including monoclonal antibodies, tyrosine kinase inhibitors, and vaccines (Zhang, 2023).

CONCLUSION

The in silico analysis results demonstrated that compounds derived from tamarind (*Tamarindus indica*) leaves possess potential anticancer activities against various types of cancer, including breast, cervical, brain, prostate, and thyroid cancers, as indicated by high Pa values based on PASS predictions. The molecular docking approach further showed that isovitexin had the lowest rerank score, suggesting a strong binding affinity toward the EGFR receptor. Therefore, the utilization of tamarind leaf compounds, particularly isovitexin, holds promise as a computationally predicted candidate for anticancer drug development.

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