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Utilizing the Pyrx Program to Conduct *in Silico* Screening of Polyphenol Compounds as Potential Inhibitors of the Epidermal Growth Factor Receptor (EGFR) in Mango Plants *(Mangifera Indica)*

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ABSTRACT

Mango (*Mangifera indica*) is a tropical plant from Asia with the potential to cure diseases including colorectal cancer. The research aimed to determine the amount of free energy (ΔG) from the polyphenol compounds of mango plants on Epidermal Growth Factor Receptor (EGFR) in silico using PyRx program with molecular docking method. The receptor used was downloaded from the Protein Data Bank (PDB) database with 1YY9 codes and the ligands used were downloaded from the KNApSAcK database. The validation of the docking method showed the RMSD value of 1.645 Å in the Alpha-Mannose; 1.381 Å in Beta-D-Mannose; 1.605 Å at 2-(Aetylamino)-2-Deoxy-A-D-Glucopyronose; and 1.334 Å in N-Acetyl-D-Glucosamine. As the standard, Cetuximab was used as a therapy for colorectal cancer. The polyphenol compounds in mango plants showed bond-free energy (ΔG) with a range of values between -8.5 kcal/mol to -6.0 kcal/mol, and the best value was Aurasperone D (-8.5 kcal/mol). Compared to Cetuximab (-6.4 kcal/mol), the value of bond-free energy (ΔG) of Aurasperoune compounds was smaller with quite a farther range of values -2.5 kcal/mol. Polyphenolic compounds discovered in Mango plants displayed potential as inhibitors for the Epidermal Growth Factor Receptor (EGFR).

Keywords: *In Silico, Mangifera indica*, Epidermal Growth Factor Receptor, *Root Mean Square Deviation*

Introduction

Cancer is an abnormal cell growth that tends to invade surrounding tissues and spread to other organs of the body that are located far away. Cancer occurs due to uncontrolled cell proliferation that occurs without limits and a purpose for the host.[1] EGF (Epidermal Growth Factor) receptors and their ligands are involved in cancer cases such as lung cancer, breast cancer, prostate cancer, brain cancer, and colon cancer.[2] In mental expression, it is proven that inhibition of EGF receptors can suppress all signs of cancer.[3] The plant polyphenolic compounds can inhibit the activity of EGFR (epidermal growth factor receptor.[4] *Mangifera indica* is a tropical fruit originating from Asia and can now be found in all tropical countries, including Indonesia.[5] The active compounds in mango fruit have been studied to have several functions, namely as antioxidants, antiproliferative, analgesic, anti-inflammatory, and antimicrobial.[6]

From several studies, it has been proven that the polyphenolic compounds contained in the extracts of several varieties of mangoes, namely Ataulfo, Haden, Kent, Francis, and Tommy Atkins mangoes, have anticancer activity.[3] Where Ataulfo and Haden showed superior effectiveness, the results of the study at a concentration of 5 mg GAE/I, Ataulfo inhibited the growth of SW-480 colon cancer cells by ~72%.[7]

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Based on the findings of this study, it has been established that Mangifera indica contains polyphenolic compounds, which leads to the conclusion that a method is needed to find out which polyphenolic compounds act as inhibitors of the Epidermal Growth Factor Receptor (EGFR).

The *in silico* method is one approach to discovering new drugs. This method is a validated protocol.[8] Where with this method the Docking process is carried out which is an attempt to align the ligand which is a small molecule to the receptor which is a large protein molecule, taking into account the nature of both.[9]

Materials and Methods

Preparation of molecular structures

The PDB file used in this study is Protein 1YY9 with a resolution of 2.605 Å obtained from the Protein Data Bank (PDB) website (https://www.rcsb.org/). Ligands and other water molecules were removed from the protein structure and the energy level of the protein structure was stabilized using Chimera software (version 1.6).

The preparation of the chemical compound or ligand model is done by downloading the chemical compound model of the mango plant (Mangifera indica) from the Knapsack Family website (http://www.knapsackfamily.com/KNApSAcK_Family/) which has the 3D MDL Molfiles [V200](*.mol) format. The format of the ligands was changed to .pdb using Vega ZZ software (version 0.8).

Protein molecular dynamics simulation and molecular docking

Ligands and proteins, saved in .pdbqt format, are processed within the PyRx program (version 3.1.0). First, settings for both the ligand and macromolecule are configured. Subsequently, the Grid Box settings are established, with a preference for maximizing size. The Vina docking process is initiated and continues until it reaches 100% completion. Within the PyRx program, the Vina Wizard is employed for docking purposes.

Following the docking procedure, the ligands and proteins that have undergone docking are visualized using the PyMOL program (version 4.6.0) and Discovery Studio 2017 (version17.2). This visualization allows for the assessment of free energy (ΔG) and the identification of the specific amino acids involved in the interaction process.

Results and Discussion

The docking process begins with validating the docking method using crystallographic ligands and optimized docking ligands. This validation was carried out to determine the closeness or similarity of the results between the crystallographic ligands and the optimized docking results so that the docking method (software used) is feasible or not for use in the next docking process.[10] The parameter observed in the validation process is the Root Mean Square Deviation (RMSD) from the redocking result between the crystallographic ligand and the optimized yield ligand on the selected active site (Figure 1). Docking software gives results that are closer to experimental results if it has an RMSD of less than 2 Å.[11] The smaller the RMSD, the closer the ligand position from the redocking result to the crystallography result.[12]

From the validation results in Table 1, it can be seen that Alpha-Mannose obtains bond-free energy (ΔG) with a value of -0.2 kcal/mol and an RMSD value of 1.645 Å; Beta-D-Mannose obtains bond-free energy (ΔG) with a value of -0.7 kcal/mol and an RMSD value of 1,381 Å; 2-(Aetylamine)-2-Deoxy-A-D-Glucopyronose obtains a bond free energy (ΔG) with a value of -1.6 kcal/mol and an RMSD value of 1.605 Å, and N-Acetyl-D-Glucosamine obtained bond free energy (ΔG) with a value of -1.3 kcal/mol and an RMSD value of 1.334 Å. From these results, it can be concluded that the values obtained are less than 2 Å, so there is a similarity between the optimized ligands and crystallographic ligands so the docking process using the PyRx program is valid.

The following is the result of the docking of polyphenolic compounds in mango plants (*Mangifera indica*) with the Epidermal Growth Factor Receptor (EGFR).

The results of the docking are evaluated by looking at the value (ΔG). Where the Gibbs free energy (ΔG) generated in the docking simulation determines the bond energy between the ligand and the receptor, The greater the affinity between the ligand and the receptor is indicated by a lower ΔG value.[13]

A small ΔG_{bind} value indicates a more stable conformation,[14] while a large ΔG_{bind} value indicates a less stable complex.[15] The RMSD value is used to determine whether the binding mode prediction is successful and it is important for docking program validation.[16] In general, the RMSD value is said to be good if it is < 2 Å.[17]

Based on the docking results listed in Table 2. Cetuximab is a comparison ligand with a ΔG value of -6.0 kcal/mol. The reason for selecting cetuximab as a comparator compound is because cetuximab is a drug that belongs to the class of drugs for cancer target therapy which will slow down or kill the growth of cancer cells. This drug is a man-made protein (monoclonal antibody) that can bind to the epidermal growth factor receptor (EGFR), which is one of the targets of colorectal cancer therapy.[18]

The results of the data above for 11 polyphenolic compounds found in mango (*Mangifera indica*) plants, the results of bond-free energy (ΔG) were obtained with a value range of -8.5 to -6.0 Kcal/mol. In the Aurasperone D compound, the lowest bond free energy values (ΔG) were obtained, namely -8.5 (kcal/mol), isomangiferin -7.5 (kcal/mol), Myrtillin -7.3 (kcal/mol), Butin and Ellagic Acid -7.2 (kcal/mol). mol), Cyanidin 3-arabinoside, Fisetin and Aphloiol/Mangiferin obtained the same values of -7.1 (kcal/mol), 1,7-Dihydroxyxnthone -6.8 (kcal/mol), Rubrofusarin with a value of -6.5 (kcal/mol), and Gallic acid with a value of -6.0 (kcal/mol). Of these 11 polyphenolic compounds, when compared with the values obtained by Cetuximab, 10 mango plant compounds have lower bond free energy (ΔG) values, so the 10 polyphenolic compounds found in mango plants have a better affinity for Epidermal Growth Factor Receptors (EGFR) versus Cetuximab.

After docking, the next step is visualization. This process is carried out to analyze the interacting bonds and bonds between ligands and amino acid residues found in the Epidermal Growth Factor Receptor (EGFR). In this process, an analysis was carried out using the PyMOL program with the help of the LigPlot program as a link to see the types of interactions and amino acid residues involved and to see the distance between the bonds formed in 3D.

Table 1: The results of the method validation of the Epidermal Growth Factor Receptor (EGFR) pdb code 1YY9

No	Chemical compounds	Free energy change (ΔG) (kcal/mol)	RMSD (Å)
1.	Alpha-Mannose	-0.2	1.645
2.	Beta-D-Mannose	-0.7	1.381
3.	2-(Aetylamino)-2-Deoxy-A-D-Glucopyronose	-1.6	1.605
4.	N-Acetyl-D-Glucosamine	-1.3	1.334

Table 2: The docking results of polyphenol compounds in mango plants (*Mangifera indica*) with Epidermal Growth Factor Receptor (EGFR) using the PyRx program with RMSD value = 0.0 Å.

No	Chemical compounds	Free energy change (ΔG) (kcal/mol)	Note
1.	Cetuximab	-6.0	(+)
2.	Aurasperone D	-8.5	(+)
3.	Isomangiferin	-7.5	(+)
4.	Myrtillin	-7.3	(+)
5.	Butin	-7.2	(+)
6.	Ellagic acid	-7.2	(+)
7.	Cyanidin 3-arabinoside	-7.1	(+)
8.	Fisetin	-7.1	(+)
9.	Aphloiol / Mangiferin	-7.1	(+)
10.	1,7-Dihydroxyxnthone	-6.8	(+)
11.	Rubrofusarin	-6.5	(+)
12.	Gallic acid	-6.0	(+)

Note: (+) : Active as an EGFR inhibitor (-): Inactive as an EGFR inhibitor

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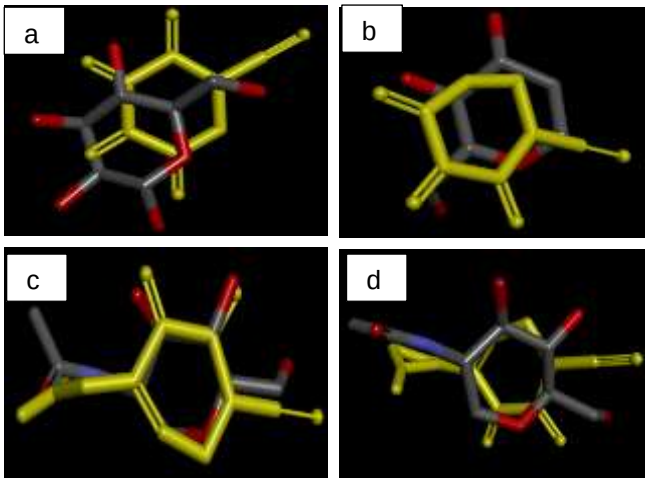


Figure 1: Overlay the position of the redocked Alpha-Mannose, Beta-D-Mannose ligands; (Aetylamine)-2-Deoxy-A-D-Glucopyronose; and N-Acetyl-D-Glucosamine with crystallographic ligands (Grey = Crystallographic results; yellow = redocking results). a = image from Alpha-Mannose redocking; b = image from Beta-D-Mannose redocking; c = image of 2-(Aetylino)-2-Deoxy-A-D-Glucopyronose redocking result; d = image of N-Acetyl-D-Glucosamine redocking results.

From Figure 2. there are two display images, namely 2D and 3D. Each image has a different meaning from each program used. The results of 2D visualization using the Discovery Studio program show several interactions that occur, namely hydrogen bonds, π-cations, π-anions, π-sulfur, alkyl, π-sigma, and π -alkyl. All bonds analyzed are non-covalent bonds. The more bonds that are formed, the more negative the value of ΔG is obtained. The π sigma and π-alkyl bonds are hydrophobic (van der Waals) bonds, while the π-cations and π-anions are joined in electrostatic bonds commonly known as salt bridges.[19]

Presented in Table 3 are the outcomes of the interaction assessment between the polyphenolic compounds within the mango plant (*Mangifera indica*) and the amino acids present in the Epidermal Growth Factor Receptor (EGFR).

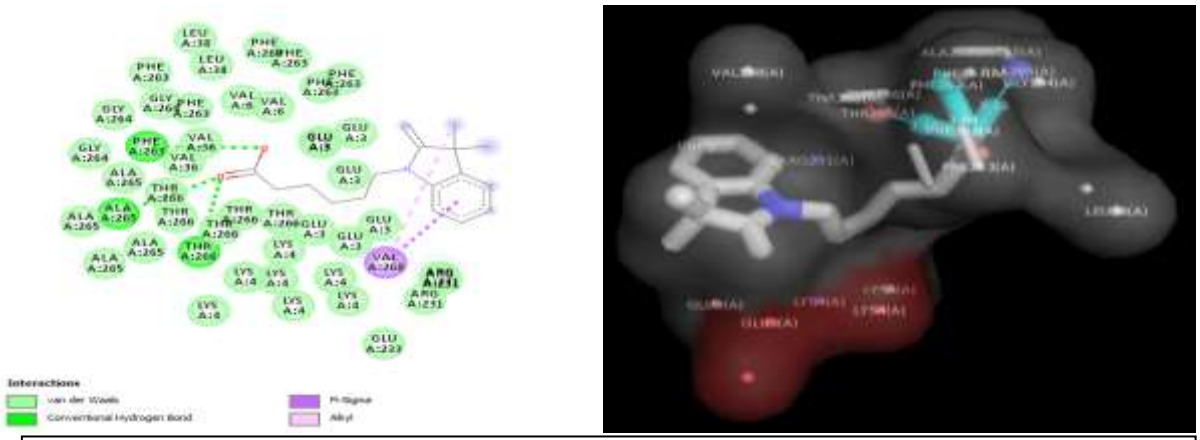
There are four parameters observed in molecular docking to determine the affinity of the ligand for the receptor, namely bond free energy (ΔG), predictive inhibition constant (PIC), amino acid residues, and the number of hydrogen bonds. As previously explained, the smaller the ΔG value and the smaller the PIC value, the higher the affinity of the ligand.[20]

Analysis of docking results and visualization includes bond free energy (ΔG) (kcal/mol), interactions of amino acid residues, both hydrogen bonding and hydrophobic interactions and Root Mean Square Deviation (RMSD).[14]

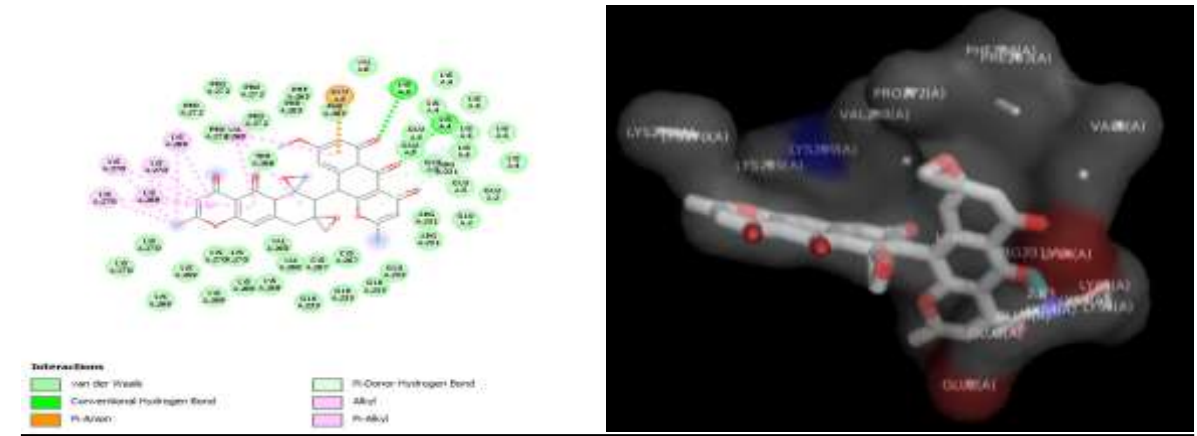
Table 3: PyMOL visualization results in the form of interactions between polyphenol compounds in mango plants (*Mangifera indica*) and amino acid residues found in the Epidermal Growth Factor Receptor (EGFR)

Compounds	Free Energy (ΔG) (kkal/mol)	Amino Acid Residue Interactions	
		Hydrogen interactions and bond spacing (Å)	Hydrophobic Interaction
Cetuximab	-6.0	Thr266 (3.24); Phe263 (3.04); Ala265 (3.11)	Arg231; Glu3; Val268; Phe263; Lys4; Thr266; Gly264; Leu38; Ala265
Aurasperone D	-8.5	Lys4 (2.83)	Val6; Lys4; Glu3; Phe263; Arg231; Glu2; Pro272; Val263; Lys269; Lys270
Isomangiferin	-7.5	Glu400 (3.15); Ser428 (2.94 & 3.26); Glu 530 (310); Arg497 (2.91)	Ser428; Glu400; Lys430; Arg509; Arg427; Glu530; Ser506; Gly508; Cys499; Arg497; Cys511
Myrtillin	-7.3	Asn33 (3.29); Val6 (3.00); Gln8 (3.26); Arg285 (3.23)	Met30; Arg29; Asn33; Asn32; Gln8; Cys7; Lys5; Arg285; Val6; Gln8; Tyr275
Butin	-7.2	Cys271 (2.95); Arg300 (2.82); Tyr275 (3.11)	Lys270; Val299; Cys271; Arg300; Val276; Val277; Gly298; Asn274
Ellagic acid	-7.2	Arg427 (2.92 & 3.11); Ser428 (3.08)	Arg427; Ser428; Arg509; Cys499; Cys511; Ser501; Glu530; Cys502; Ser506
Cyanidin 3-arabinoside	-7.1	Leu120(2.89 & 3.07); Glu118 (2.79; 2.87; & 3.26); Arg198 (2.98); Asn210 (2.91); Arg228 (3.25)	Ser146; Ser145; Lys188; Glu118; Leu120; Lys 188; Gly197; Arg228; Arg198; Asn210; Cys212
Fisetin	-7.1	Cys271 (2.77); Tyr275 (3.09); Arg300 (2,94; 3.33; 3.24; & 3.27); Gly298 (3.25); Val299 (3.26); Asn274 (2.96)	Lys270; Val299; Cys271; Gly; 298; Val277; Arg300; Asn274; Glu295; Arg273
Aphloiol / Mangiferin	-7.1	Gly508 (3.27); Cys499 (2.90); Arg427 (3.11 & 3.22); Cys502 (3.14); Ser529 (3.34)	Ser428; Lys430; Arg509; Gly508; Cys502; Asn528; Val500; Ser501; Ser529

1,7-Dihydroxyxnthone	-6.8	Asn580 (3.20); Asn579 (3.12)	Asn580; Thr239; Thr239; Pro241; Pro242; Glu258; Glu578; Leu245
Rubrofusarin	-6.5	Ser428 (2.79); Arg497(2.78)	Ser428; Arg509; Arg427; Arg497; Val500; Ser501; Cys502; Cys511
Gallic acid	-6.0	Lys4 (3.20 & 3.28); Glu60 (2.80 & 2.79); Ala265 (3.11)	Lys4; Glu3; Val; Phe263; Arg231; Thr266; Gly264; Glu60; Val36; Ala265



Amino Acid Interactions with Cetuximab



Amino Acid Interaction with Aurasperone D

Figure 2: Visualization results of Cetuximab, Aurasperone D and with the Discovery Studio program (left), and the PyMOL program (right).

From the data in Table 3, it can be seen that each compound interacts with almost different amino acids and obtains different hydrogen bond distances. Where Cetuximab which acts as a comparator obtains a bond-free energy value (ΔG) of -6.0 kcal/mol with the interaction of hydrogen Thr266 with a bonding distance of 3.24 Å, Phe263 with a bonding distance of 3.04 Å and Ala265 with a bonding distance of 3.11 Å, for hydrophobic interactions which are received cetuximab namely Arg231; Glu3; Val268; Phe263; Lys4; Thr266; gly264; Leu38; Ala265. Of the 11 polyphenolic compounds in mango (*Mangifera indica*), Auresperon D is the compound that has the smallest bond-free energy (ΔG) value of -8.5 kcal/mol with the interaction of hydrogen Lys4 with a bond distance of 2.83 Å and hydrophobic interaction Val6; Lys4; Glu3; Phe263; Arg231; Glu2; Pro272; Val263; Lys269; Lys270. For the Gallic acid compound, the bond free energy value (ΔG) is the same as cetuximab, namely -6.0 Kcal/mol, and the hydrogen bonds formed are Lys4 with a bond distance of 3.20 & 3.28 Å; Glu60 with a bond distance of 2.80 & 2.79 Å; Ala265 with a bond distance of 3.11 Å. As for the hydrophobic interaction, Arg705; Leu1017; Ile1018; Leu703; Ala767; Arg776; Asp770.

From the results of the interaction of amino acid residues in the Auresperon D compound when compared with the amino acid residues produced by Cetuximab, there are 4 interactions of the same amino acid residues, namely Lys4; Glu3; Phe263; and Arg231. Whereas in the Gallic acid compound, 6 amino acid interactions are the same as the amino acid residues produced by Cetuximab, namely Lys4; Glu3; Val6; Phe263; Arg231; Thr266; and Gly264. So the compounds Auresperon D and Gallic acid show similar activity with the comparator compound, namely Cetuximab is a Gallic acid compound. The tested ligands with amino acid residues and hydrogen bonds that are close to natural ligands show similar interactions in this case and describe similar activities.[21] Hydrogen bonds are intermolecular interactions formed between H atoms that are covalently bonded to high electronegativity atoms (such as F, O, and N) and high electronegativity atoms in other molecules. This bond is the strongest intermolecular bond.[22] Hydrogen bonds can occur between intermolecular and intramolecular. The strength of the hydrogen bond is affected by the distance between the bonds formed. The shorter the distance formed, the stronger the bond strength.[23] A good range of hydrogen bonds is between 2.5-3.5 Å.[24]

Conclusion

Based on the results of the research conducted, it can be concluded that of the 11 polyphenol compounds found in mango (*Mangifera indica*) plants, the two compounds with the best ΔG values were obtained, namely Aurasperone D (-8.4 kcal/mol). Compared to Cetuximab (-6.4 kcal/mol), the value of the bond free energy (ΔG) of Aurasperone D is smaller and the range of values is quite far. This shows that the polyphenolic compounds from the mango plant (*Mangifera indica*) have the potential to act as Epidermal Growth Factor Receptor (EGFR) inhibitors.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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