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Literature Review : In Silico Study Of Lung Anticancer Proteins

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ABSTRACT

Cancer is a disease caused by rapid and uncontrolled cell proliferation. Cancer is a massive disease characterized by rapid and uncontrolled cell proliferation. Cancer cells will continue to affect other cells around them until all tissues with cancer damage organs and nerves. One type of cancer with high cases in Indonesia is lung cancer. This cancer is a type of tumor whose source is the epithelial lining of the bronchial lung branches. Generally, therapy for the treatment of lung cancer is radiation, chemotherapy, surgery, and hormone therapy. In silico testing is a type of study with a computational approach to predict the activity of potential compounds as drugs. This article uses a type of literature review research with a total of 15 reference materials indexed on Google Scholar.

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1. INTRODUCTION

Cancer is a disease caused by rapid and uncontrolled cell proliferation. Cancer is a massive disease characterized by rapid and uncontrolled cell proliferation. Cancer cells will continue to affect other cells around them until all tissues with cancer damage organs and nerves [1]. Uncontrolled cell growth of cancer cells will result in tumors and can attack other parts of the body. According to the International Agency for Research on Cancer (IARC) it is known that in 2012 cancer cases worldwide were around 14 million which caused the number of deaths reaching 8 million. Types of cancer consist of liver, stomach, lung, colorectal, and breast cancer [2]. The percentage of lung cancer ranks highest in Indonesia in 2019, which is around 12.6% of 207,210 cases. Lung cancer is caused by a mutated Epidermal Growth Factor Receptor (EGFR) gene. In 2012 the type of cancer that was ranked third was colorectal cancer [3].

One type of cancer with high cases in Indonesia is lung cancer. This cancer is a type of tumor whose source is the epithelial lining of the bronchial lung branches. The number of cancer cases in the world is around 13%. According to data from the World Health Organization (WHO), men are the sex with the most lung cases in Indonesia, lung cancer ranks fifth in women. The cause of lung cancer can come from smoking with arsenic triggers and air pollution [4]. Generally, therapy for the treatment of lung cancer is radiation, chemotherapy, surgery, and hormone therapy. This type of treatment raises quite large unwanted effects for patients [5]. Other studies have stated that cancer therapy is a combination and the treatment differs at the stage level and is adapted to the conditions and needs of cancer sufferers. Surgery and radiotherapy are usually effective for patients with early cancer. Combined therapy of surgery, radiotherapy and chemotherapy is given to metastatic cancer patients. The radiation method has adverse effects, namely interfering with blood production, being cardiotoxic, and degrading sperm quality in men. Chemotherapy is reported to cause nausea to anorexia in patients. Some drugs given in cancer therapy cannot be given simultaneously with other drugs because they will strengthen their work so that they are often the cause of death. This huge negative impact causes cancer sufferers to switch to cancer treatments that come from nature [6].

So far, testing of compounds that have the potential to be used as drugs consists of preclinical testing and clinical testing. However, these two types of research are less effective in terms of time and cost, so it is necessary to make compound predictions in order to minimize the risk of existing

failures and future tests can run effectively. This prediction test is called in silico testing. In silico testing is a type of study with a computational approach to predict the activity of potential compounds as drugs. In silico testing can determine the activity of potential compounds that will be used as drugs without compound synthesis so that they can be more effective in terms of time, cost, and effort expended [3]. Molecular docking studies are a way of using a computational approach to search for a geometrically and energetically suitable ligand to the binding site of a target protein. Molecular docking is used to look for a description of the interaction of the ligand with the target protein which is usually done in vitro, but via a computer. This molecular docking predicts precisely the binding of potential drug candidates that have specific small molecules to the target protein to predict the affinity and activity of these molecules [7].

2. METHOD

This article uses a type of literature review research by searching for the keywords "docking lung cancer", "molecular docking", "search for new lung cancer drugs", "docking lung cancer" and "new lung cancer drug design" on Google Scholar. The number of articles used as reference material is 15 articles that have been indexed on Google Scholar and pubmed.

3. RESULTS AND DISCUSSION

Molecular docking is a way to identify strategic proteins that play a role in causing a disease, so it is often used for in silico testing. In this tethering, the binding interaction between the protein and the ligand is seen to predict its position and orientation. The results obtained from molecular docking tests are very diverse which can be adjusted according to the purpose of the test. Parameters observed include the level of conformational stability between protein macromolecules and ligands, RMSD which is a positional deviation value which is usually used for the validity of the method, and the type of hydrogen bonding. Acceptable RMSD when <2A. Protein binding site is the area of the protein binding site to the molecule that will affect the activity of the protein concerned [6]. Other physico-chemical parameters determined by the Lipinsky rule of five for a compound that can be bonded molecularly if the molecular weight is <500g/mol, ClogP<5, the number of hydrogen bonds is not more than 5, the acceptors of hydrogen bonds are less than 10, the molar refractivity is 40-130 . If the bond free energy value is lower then the binding affinity of the compound with the receptor is better. The constant value of the inhibition is lower, the more effective the inhibitory activity is [8].

Conformation is where the initial coordinates of the atom change to new coordinates, the speed of movement is calculated in units of time. This so-called stable molecular conformation is characterized by a low energy yield. Hydrogen bonds are the main bond interactions that keep proteins stable in the body. In molecular docking studies, hydrogen bonding is a parameter that the compound is stable. Parameters if the positive control matches the amino acid residues can indicate that the compound being tested has an almost similar or even better inhibitory ability than the positive control. Changes in the interaction between the receptor and the ligand result in amino acid residues from simulated molecular docking with different molecular dynamics. If the amino acid residues are the same before and after the molecular dynamics, it means that the test compound can be said to be stable and resistant to thermodynamic changes [2]. RMSD values below 2A, binding energy and low inhibition constants are also parameters for the success of molecular docking [4].

Approximately 40-80% of non-small lung cancer cases have excess cell expression on the EGFR so that this receptor can be used as a target for lung cancer therapy. Epidermal Growth Factor Receptor (EGFR) is a receptor protein that belongs to the protein tyrosine kinase ERBB-1 in the form of a transmembrane glycoprotein which is on chromosome number 7p12. The role of this EGFR receptor is to trigger apoptosis, cell division, angiogenesis, and invade cancer cell metastases [6]. Gefitinib was used as a positive control because it is a drug that is usually used in lung cancer. Gefitinib binds to the tyrosine kinase domain on the EGFR thereby interfering with receptor autophosphorylation which causes signal transduction to not occur. The chalcone analog compound and the positive control gefitinib were observed in molecular dynamic simulations including the conformational energy of the compounds, hydrogen binding, and comparing the residues resulting from docking and molecular dynamics to find stable compounds against changes.

The two docking amino acid residues are Leu54, Ile99, Met62, Val93 and Ile61. While the molecular dynamic residues are Tyr60, Leu85, Leu37, Phe86, Leu81, Leu33, Gln59, Arg105, Asp84, Leu82, Leu54, Ser78, Asn79, Leu85, Asp80 so that the number of amino acid matches is 1. In compound 5 the molecular anchorages are Leu57 and Leu while molecular dynamics Tyr100, Glu95, Gln72, Arg65, Tyr104, Lys94, Met62, Tyr67, Asp68, Ile61, Leu57, Leu56, Ile103, His96, Gly58, Arg97, Ser92, Leu54, Lys98, Val93, Ile99 number of amino acid matches 6. Residue the molecular anchoring of compound 6 is Ile99, Val93, Ile61, and Leu54 while the molecular dynamics are Phe86, Leu82, Pro89, Phe91, Met62, Val93, Lys94, Leu57 the number of amino acid matches is 1. Gefitinib amino acid residues are Gly58, Asn79, Leu54, Ser78, Asp84, Leu81, Asp80, Met62, Gln72, Tyr67, Val93, Val75, Ile61, Leu57 while the molecular dynamics of Asn79, Asp80, Asp84, Gly83, Thr63, Leu82, Met62, Lys94, Leu54, Val93, Ser78 and the number of amino acid matches is 7. In compounds 2, 5, and 6 hydrogen bonds are formed with conformational energies of -4,042.95, -4,050.14, -4,034.10 respectively from molecular docking. Compound 5 has potential as an anticancer lung. Compounds 2 and 6 are unstable because they do not meet the parameters of conformational energy values, hydrogen bonds, the number of matches of amino acids to gefitinib, the number of matches of amino acids resulting from molecular docking and molecular dynamics [2].

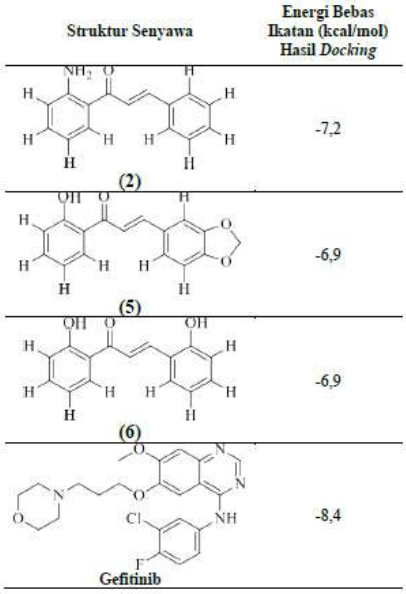


Fig 1. Structure of Chalcone Analogous Compounds As Ligand

The bond energy between the native ligand and the macromolecule is -7.13 kcal/mol, the inhibition constant is 5.89, RMSD is 1.03A. In visualizing the results of molecular docking between macromolecules and native ligands, it can be seen that there are hydrogen, van der Waals, Pi-Sigma, p-sulfur, pi-alkyl and alkyl bonds. The hydrogen bonded compound is CYS A:797. Meanwhile the interaction between the macromolecules and the test ligands, the bond energy is 4.71 kcal/mol, RMSD 1.41A, the inhibition constant is not available, but there is a bond between the macromolecules and the test ligands in the presence of GLU B: 906, alkyl, and van der Waals hydrogen bonds. . This indicates that the tested ligand 2,6-dimethylocta-3,5,7-trien-2-ol is not as good as the native YUN ligand so that this compound has the potential to be used as a lung cancer treatment but is not very effective [4].

In the interaction of the 4LRM macromolecule with the native ligand, the binding bond is -8.3 kcal/mol, RMSD 3.17A, the type of bond that occurs is a hydrogen bond. The linked amino acids are Met796 and CYS800 involving residues Asp803, Gly799. Leu718, Thr857, Gln794, Lys745, Glu762. Ala743, Leu795, Thr793, Val726, and Leu847. The interaction between 4LRM and the test ligand 3,5,7-Octatrien -2-Ol,2,6- Dimethyl the binding bond is -8, RMSD 1.97A, the type of bond is hydrogen, the linked amino acids are Met796 and CYS800 involving the residue Asp803, gly799. Leu718, Thr857, Gln794, Lys745, Glu762. Ala743, Leu795, Thr793, Val726, and Leu847 [6].

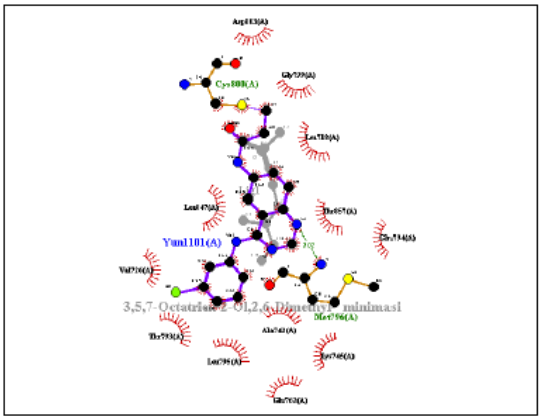


Fig 2. Amino acid residues at the receptor binding site of the EGFR protein

The IQG4 receptor energy affinity value for the native ligand was -3 kcal/mol, for the tested ligand -4.4 kcal/mol. The energy affinity value for the native 21OK receptor ligand is -6.6 kcal/mol, the tested ligand is -6.4 kcal/mol. The energy affinity value of the 2ITO native ligand receptor is -7 kcal/mol, the tested ligand is -6.5 kcal/mol. The energy affinity value for the native 2VCJ receptor ligand is -5.9 kcal/mol, while the tested ligand is -5 kcal/mol. The energy affinity value for the native 3CF9 receptor ligand is -5.2 kcal/mol while the tested ligand is -4.6 kcal/mol [1].

In compound 1 the energy affinity is -7.3 kcal/mol, RMSD is 0, the hydrogen bond interaction is Thr49 on the OCH3 group, and the amino acid residues Lys51, Ala21, Tyr67. Compound 2 has an energy affinity of -7.2 kcal/mol, RMSD 0, the hydrogen bond interaction is Leu54 on the NH2 group and the amino acid residues Ile99, Ile61, Met62, Val93. Compound 3 has an energy affinity of -7.1 kcal/mol, RMSD 0, hydrogen bond interactions are not formed, and the amino acid residues are Leu54, Ile99, Ile61, Met62, Val93. Compound 4 has an energy affinity of -7 kcal/mol, RMSD 0, the hydrogen bond interaction is Lys51 in the C=O group, amino acid residues Ser17, Ile19, Asp68. Compound 5 has an energy affinity of -6.9 kcal/mol, RMSD 0, the hydrogen bond interaction is Leu54 on the OH group, amino acid residues Leu57, Ile99, Ile61, Met62, Val93. Compound 6 has an energy affinity of -6.9 kcal/mol, RMSD 0, the hydrogen bond interaction is Leu54 on the OH group, amino acid residues Ile99, Ile61, Val93. Compound 7 has an energy affinity of -7 kcal/mol, RMSD 0, hydrogen bond interactions are not formed, amino acid residues Leu54, Tyr67, Ile99, Ile61, Val93. Compound 8 has an energy affinity of -6.9 kcal/mol, RMSD 0, hydrogen bond interactions are not formed, amino acid residues Leu54, Tyr67, Ile99, Ile61, Val93, Met62. Compound 9 has an energy affinity of -7 kcal/mol, RMSD 0, hydrogen bond interactions are not formed, amino acid residues Leu54, Tyr67, Ile99, Ile61, Val93, His96, Gln72. Compound 10 energy affinity -7 kcal/mol, RMSD 0, hydrogen bond interaction not formed, amino acid residues His73, Gln72, Val93, His96, Ile99, Tyr100. Gefitinib as a positive control has an energy affinity of -7.8 kcal/mol, RMSD 0, the hydrogen bond interaction is Leu54 on the NH2 group and the amino acid residues Ile61, Val93, Met62, Asp84, Asp80, Asn79 [5].

Gingerdiol BM 296.40 gram/mol, ClogP 3.39, the number of hydrogen bond donors is 3, the number of hydrogen bond acceptors is 4, the molar refractivity is 85.51. Gingerdione BM 292.37 gram/mol, ClogP 3.14, number of hydrogen bond donors 1, number of hydrogen bond acceptors 4, molar refractivity 83.59. Gingerol BM 294.39 gram/mol, ClogP 3.48, the number of hydrogen bond donors is 2, the number of hydrogen bond acceptors is 4, the molar refractivity is 84.55. Hexahydrocurcumin BM 374.43 gram/mol, ClogP 3.23, the number of hydrogen bond donors is 2, the number of hydrogen bond acceptors is 6, the molar refractivity is 102.79. Paradol BM 278.39 gram/mol, ClogP 3.65, the number of hydrogen bond donors is 1, the number of hydrogen bond acceptors is 3, the molar refractivity is 83.39. Shogaol BM 276.37 gram/mol, ClogP 3.28, the number of hydrogen bond donors is 1, the number of hydrogen bond acceptors is 3, the molar refractivity is 82.91. Zingerone BM 194.23 gram/mol, ClogP 2.09, the number of hydrogen bond donors is 1, the number of hydrogen bond acceptors is 3, the molar refractivity is 54.54. The RMSD value at rank 1 is 0.92A and the energy binding value is -9.65. The total energy of the Gingerdiol compound is -6.96

kcal/mol while the inhibition constant is 7.87. The total energy of the gingerdione compound is -7.03 while the inhibition constant is 7.09. The total energy of the gingerol compound is -7.23 while the inhibition constant is 4.98. The total energy of the hexahydrocurcumin compound is -8.16 while the inhibition constant is 1.05. The total energy of the paradol compound is -7.39 while the inhibition constant is 3.85. The total energy of the shogaol compound is -7.68 while the inhibition constant is 2.35. The total energy of the zingeron compound is -5.77 while the inhibition constant is 58.51. The total energy of the native ligand is -9.65 while the inhibition constant is 84.12 nm. In the gingerdiol compound residue LYS129, the bond type is Hydrogen, the distance is 2.871. LEU83 residue, Hydrogen bond type, spacing 2.722.

Residue THR165, Hydrogen bond type, spacing 2.828. HIS84 residue, Hydrogen bond type, 1.919 range. ILE10 residue, Hydrophobic bond type, range 3.724. Residue ALA144, Hydrophobic bond type, spacing 3.516. LEU134 residue, Hydrophobic bond type, spacing 4.474. LEU134 residue, Hydrophobic bond type, range 4.863. The gingerdione compound contains residue LYS129, Hydrogen bond type, distance 2.871. LEU83 residue, Hydrogen bond type, spacing 2.779. Residue THR165, Hydrogen bond type, spacing 2.828. ASP86 residue, Hydrogen bond type, 2.327 spacing. HIS84 residue, Hydrogen bond type, spacing 3.385. ALA31 residue, Hydrophobic bond type, spacing 4.351. Residue VAL18, Hydrophobic bond type, spacing 3.525. PHE80 residue, Hydrophobic bond type, spacing 4.338. ILE10 residue, Hydrophobic bond type, range 5.128. LEU134 residue, Hydrophobic bond type, range 5.272. The gingerol compound contains residue LYS129, Hydrogen bond type, distance 2.871. LEU83 residue, Hydrogen bond type, 2.725 spacing. ASP86 residue, Hydrogen bond type, 2.915 spacing. Residue THR165, Hydrogen bond type, spacing 2.828. HIS84 residue, Hydrogen bond type, 2.334 spacing. GLU81 residue, Hydrogen bond type, spacing 1.931. ASP86 residue, Hydrogen bond type, 3.018 spacing. ILE10 residue, Hydrophobic bond type, range 3.852. ALA144 residue, Hydrophobic bond type, spacing 3.818. The hexahydrocurcumin compound contains LYS129 residues, Hydrogen bond type, spacing 2.871. LEU83 residue, Hydrogen bond type, 2.787 spacing. Residue THR165, Hydrogen bond type, spacing 2.828. LEU83 residue, Hydrogen bond type, 2.017 spacing. ILE10 residue, Hydrogen bond type, 2.046 spacing. Residue ASP145, Hydrogen bond type, spacing 1.843. ASP86 residue, Hydrogen bond type, 3.404 spacing. GLN31 residue, Hydrogen bond type, spacing 3.228. ILE10 residue, Hydrophobic bond type, range 3.228. PHE80 residue, Hydrophobic bond type, 5.303 spacing. GLN85 residue, Hydrophobic bond type, range 5.158. Residue ALA144, Hydrophobic bond type, spacing 4.131.

The paradol compound contains residue LYS129, Hydrogen bond type, spacing 2.871. LEU83 residue, Hydrogen bond type, 2.953 spacing. ASP86 residue, Hydrogen bond type, 3.004 spacing. Residue THR165, Hydrogen bond type, spacing 2.828. HIS84 residue, Hydrogen bond type, spacing 2.322. ASP86 residue, Hydrogen bond type, 3.034 spacing. ILE10 residue, Hydrophobic bond type, range 3.906. Residue ALA144, Hydrophobic bond type, spacing 3.998. The shogaol compound contains residue LYS129, Hydrogen bond type, spacing 2.871. LEU83 residue, Hydrogen bond type, 2.832 spacing. ASP86 residue, Hydrogen bond type, 3.086 spacing. Residue THR165, Hydrogen bond type, spacing 2.828. HIS84 residue, Hydrogen bond type, 2.203 spacing. GLN85 residue, Hydrogen bond type, spacing 3.03. ASP86 residue, Hydrogen bond type, 3.058 spacing. ILE10 residue, Hydrophobic bond type, range 3.807. Residue ALA31, Hydrophobic bond type, spacing 3.659. Residue ALA144, Hydrophobic bond type, spacing 3.371. Residue VAL18, Hydrophobic bond type, spacing 3.68. PHE80 residue, Hydrophobic bond type, spacing 4,111. PHE80 residue, Hydrophobic bond type, spacing 4.237. The zingeron compound contains LYS129 residues, Hydrogen bond type, spacing 2.871. LEU83 residue, bond type n Hydrogen, distance 2.689. ASP86 residue, Hydrogen bond type, 3.092 spacing. Residue THR165, Hydrogen bond type, spacing 2.828. HIS84 residue, Hydrogen bond type, 2.226 spacing. ASP86 residue, Hydrogen bond type, 3.057 spacing. ILE10 residue, Hydrophobic bond type, range 3.824. It can be said that all the amino acids in the vanilloid compound play a role in the constituent of the active site of the EGFR exon 20 receptor [8].

Grid box used from native ligand testing X axis = -22.748 Å, Y = 2.4218 Å, Z = -11.7748 Å with grid size X = 10.0558 Å, Y = 10.7264 Å, Z = 9.5328 Å for 5AUX on X axis = -22.7927 Å, Y = 2.4578 Å, Z = -12.1170 Å and grid X = 9.4990 Å, Y = 10.7387 Å, Z = 7.1328 Å for 5AV3 . In the 5AUX protein, the RMSD value was 1.476 A. The interacting amino acid residues included Val96,

Glu94, Leu95, Ala40, Val27, Gly20, Ser21, Gly22, Asp161, Lys42, Leu19, Ile160. The same interaction was shown by testing the KMP co-crystal ligands, namely residues Val96, Glu94 (hydrogen bonds). The bond affinity value of anyata 5AUX with the native ligand is -8.8 kcal/mol while the bond affinity value with the kaempferida test ligand is -8 kcal/mol. The interactions of amino acid residues with kaempferida are Leu19, Val96, Glu94, Leu93, Ala40, Ile77, Ile160, Asp161, Gly22, Ser21, Gly20, Met146. In the 5AV3 protein, the RMSD value was 1.731 A. The interacting amino acid residues included Val96, Glu94, Leu95, Leu19, Met146, Gly20, Gly22, Ser21, Lys42, Asp161, Ile160, Val27, Ala40. The same interaction was shown by testing the KMP co-crystal ligands, namely residues Leu19, Ser21, Asp161 (hydrogen bonds). The bond affinity value of anyata 5AV3 with the native ligand is -9 kcal/mol while the bond affinity value with the kaempferida test ligand is -8 kcal/mol. The interactions of amino acid residues with kaempferida are Asp161, Ala40, Ile160, Glu94, Ile77, Val96, Met146, Leu19, Val27, Gly20, Ser21, Gly22 [9].

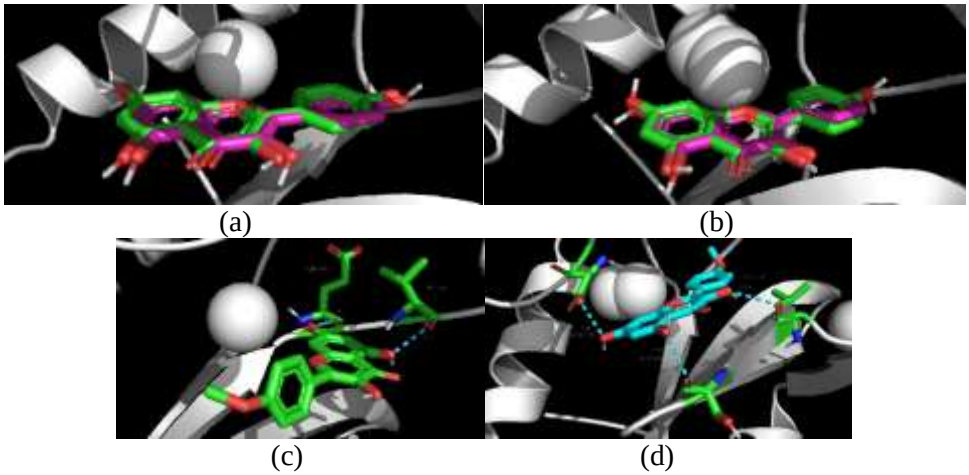


Fig 3. (a) 3D visualization of KMP alignment results on 5AUX; (b) 5AV3. KMP redocking (green), KMP co-crystal (purple); (c) 3D visualization of the interaction of kaemferida with 5AUX; (d) 5AV3 through hydrogen bonds. Hydrogen bonds are indicated by dashed lines in turquoise

4LRM protein with D-alpha-Tocopherol ligand has a bond affinity value of -4.6 kJ/mol, RMSD 1.760 A, hydrophobic bond type with amino acid residues CysB:800, ValB:726, LysB:745, AlaB:763, LeuB:718 , LeuB:847, MetB:766, Arg:B844. The 4LRM protein with the Evodiamine ligand has a bond affinity value of -7 kJ/mol, RMSD 1.426 A, hydrogen bonds with AspB:858 amino acid residues, and hydrophobic bonds with LeuB:718, LeuB:847, AlaB:743, LysB:745 amino acid residues. , AspB:858. The 4LRM protein with native YUN B 1101 ligand has a bond affinity value of -7.3 kJ/mol, RMSD 2.707, hydrophobic bond type with residues AlaB:743, ValB:726, LysB:745, and electrostatic bond with LysB:745. 5USQ protein with D-alpha-Tocopherol ligand has a bond affinity value of -7.6 kJ/mol, RMSD 2.176 A, type of hydrogen bonding with amino acid residues AspA:290, hydrophobic bonds with amino acid residues PheA:262, TyrA:249, LeuA: 278, LeuA:260, LysA:232, ValA:219, IleA:211, AlaA:230, TyrA:282. The 5USQ protein with Evodiamine ligand has a bond affinity value of -6.5 kJ/mol, RMSD 2.494 A, hydrophobic bonds with amino acid residues IleA211, ValA219, AlaA230. The 5USQ protein with native ligand 8LY A 500 has a bond affinity value of -9.6 kJ/mol, RMSD 2.935, type of hydrogen bonding with GlyA:L212 residues and hydrophobic bonds with residues ValA:219, LeuA:340, AlaA:350 [3].

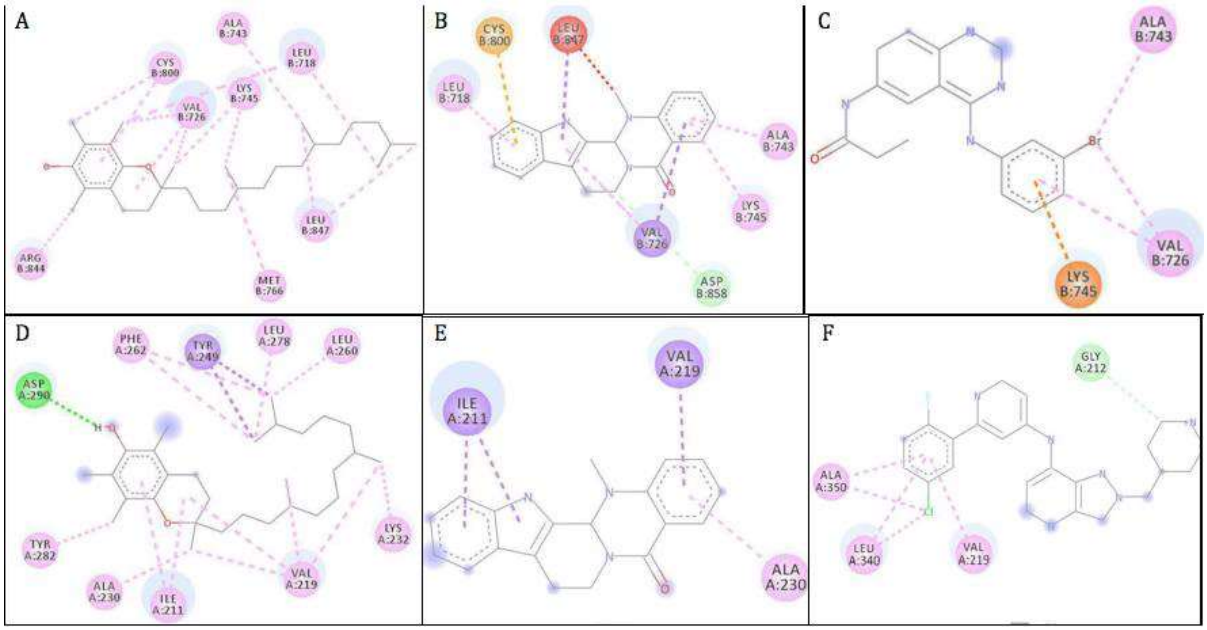


Fig 4. Visualization of EGFR Docking Results with D-alpha-Tocopherol (A), evodiamine (B), YUN B 1101 (C) and ALK with D-alpha-Tocopherol (D), evodiamine (E), 8LY A 500 (F)

The RMSD value for the native ligand is 0.91 A. The central grid box value is x = 24.407, y = 9.151 z = -0.636 with a distance of 0.375 Å. Trigonelin has a BM of 137.14, a log P value of -4.14, 0 hydrogen bond donors, and 3 acceptor hydrogen bonds. Physico-chemically, cyanidin has a molecular weight of 287.247, log P 2.61, 5 hydrogen bond donors, 5 hydrogen bond acceptors. Cyanidine has an energy affinity of -9.35 kcal/mol, inhibition constant 140.16, and 6 hydrogen bonds. with residues Met793, Gln791, Thr854, Asp855, Lys745. Delfinidin physico-chemically has BM 303.246, log P 2.33, number of hydrogen bond donors 6, number of hydrogen bond acceptors. hydrogen bonds 8 with residues Met793 (2), Leu718 (2), Gln791, Thr854 [7].

Natural ligands have an energy affinity of -9.18 kcal/mol, an inhibition constant of 0.21708, a number of hydrogen bonds of 4, with 12 amino acid residues. Peonidin has an energy affinity of -7.13 kcal/mol, an inhibition constant of 5.97, the number of hydrogen bonds is 1, with 3 amino acid residues. Delfinidin has an energy affinity of -7.21 kcal/mol, an inhibition constant of 5.12, the number of hydrogen bonds is 1, with 3 amino acid residues. Aurantinidin has an energy affinity of -5.20 kcal/mol, an inhibition constant of 154.59, the number of hydrogen bonds is 1, with 3 amino acid residues. Gefitinib has an energy affinity of -6.36 kcal/mol, an inhibition constant of 21.62, the number of hydrogen bonds is 1, with 9 amino acid residues. Europinidine has an energy affinity of -7.37 kcal/mol, an inhibition constant of 3.95, number of hydrogen bonds 4, with 8 amino acid residues. Capensinidine has an energy affinity of -5.09 kcal/mol, inhibition constant of 187.95, number of hydrogen bonds is 2, with 8 amino acid residues. Cinidin has an energy affinity of -6.51 kcal/mol, inhibition constant of 17.04, number of hydrogen bonds 5, with 8 amino acid residues. Rosinidin has an energy affinity of -6.73 kcal/mol, an inhibition constant of 11.67, number of hydrogen bonds 4, with 9 amino acid residues [11].

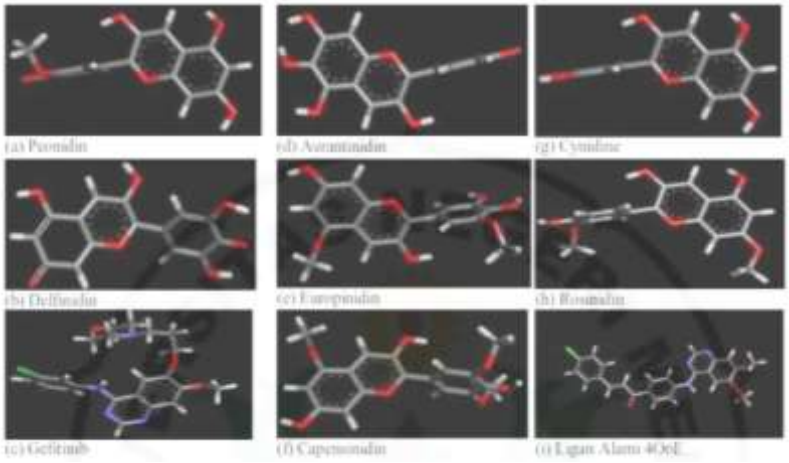
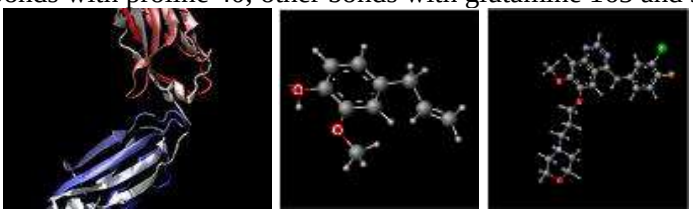


Fig 5. 3D Test Compound Structure

The RMSD value obtained was 1.0811 A. Native ligand bond energy value -57.2906 kcal/mol, Octadec-9-enoic acid bond energy -72.4518 kcal/mol, Hexadecanoic acid (palmitic acid) bond energy value -70.2136 kcal/ mol, Octadecanoic acid (stearic acid) bond energy value -72.2362 kcal/mol, Benzene, 1-ethyl-3-methyl bond energy value -49.6322 kcal/mol [12]. 1,3,4-Eugenol with macromolecule Her-2 surface interaction value of 411.564, bond affinity energy -4.16 kcal/mol, and inhibition constant 895.67 µM. In eugenol the type of covalent bond with glycine 38, hydrophobic bonds with proline 40 and phenylalanine 83, other bonds with lysine 103, glutamine 165, and threonine.

Gefitinib with Her-2 has a molecular surface interaction value of 668.342, a bond affinity energy value of -7.05 kcal/mol, and an inhibition constant of 225.70 µM. Types of hydrogen bonds with valine 163, halogen bonds with aspartic acid 167 and glycine 166, polar covalent bonds with serine 162, hydrophobic bonds with proline 40, other bonds with glutamine 165 and serine 168 [13].



(a) (b) (c)

Fig 6. Three Dimensional Molecular Image: A. Her2 Receptor, B. Eugenol (1,3,4 Eugenol), C. Gefitinib (Protein Data Bank A) ID. 1n8z; B) I.D. 2QW8; C) I.D. 4KWQ)

Paclitaxel has an energy affinity value of -125,918 kcal/mol, type of hydrogen bond with Gln 195, Gln 347 and Gln 946 residues. Docetaxel has an energy affinity value of -94,971 kcal/mol, type of hydrogen bond with Gln 913. Gemcitabine has an energy affinity value of -44,170 kcal/mol, type of hydrogen bonding with Asp 188 and Glu 875 [14].

The interaction of scopoletin with 6DUK produces an energy affinity value of -8 kcal/mol, the type of hydrogen bonding with residues gly-614 and SER-6. The interaction of scopoletin with 6DUK produces an energy affinity value of -8 kcal/mol, the type of hydrogen bonding with residues gly-61415. The interaction of scopoletin with 3OCB produces an energy affinity value of -7.12 kcal/mol, the type of hydrogen bonding with residues TYR-175, ASN-231, LYS-284, TYR-229. The interaction of scopoletin with 1NFI produces an energy affinity value of -6.97 kcal/mol, a type of hydrogen bonding with residue Arg-140, tyr-181 [15].

4. CONCLUSION

Molecular docking is a way to identify strategic proteins that play a role in causing a disease, so it is often used for in silico testing. Parameters observed include the level of conformational stability between protein macromolecules and ligands, RMSD which is a positional deviation value which is

usually used for the validity of the method, and the type of hydrogen bonding. Acceptable RMSD when <2A. Protein binding site is the area of the protein binding site to the molecule that will affect the activity of the protein concerned [6]. Other physico-chemical parameters determined by the Lipinsky rule of five for a compound that can be bonded molecularly if the molecular weight is <500g/mol, ClogP<5, the number of hydrogen bonds is not more than 5, the acceptors of hydrogen bonds are less than 10, the molar refractivity is 40-130 . If the bond free energy value is lower then the binding affinity of the compound with the receptor is better. The lower the inhibition constant value, the more effective the inhibitory activity will be.

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