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Molecular docking test on plants fruit pomegranate red (Punica granatum L.) as disease inhibitor agent heart (cardiovascular)

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ABSTRACT

Work fatigue is one of the occupational health and safety problems. This study was to evaluate the potential of active compounds from pomegranate plants (Punica granatum L.) as heart disease inhibitor agents through a Molecular docking approach. The method used involved 3D structural analysis of four active compounds – Quercetin, Caffeic acid, Ellagic acid, and Phenol – in this plant which were downloaded from PubChem and processed using Swiss Target Prediction, Super Prediction, PyMol, Pyrx software. The interaction between compounds and biological targets in this case Clopidogrel, was studied to determine binding energy, binding affinity and stability. The results showed the Ellagic acid and Quercetin had significant interaction with the lowest binding energy of -7.8 kcal/mol and -8.7 kcal/mol and the lowest RMSD value of 0 (Å) so that this can be said to have good interaction stability with the protein target. The 3D molecular structure of these two compounds also shows the presence of hydrogen bonds and effective interactions with amino acids as well as low toxicity and favorable affinity energy. Based on these results, Ellagic acid and Quercetin were identified as potential candidates in the development of drugs to treat heart disease (cardiovascular). This study is expected to review the potential of active compounds in pomegranates through the insilico method, which can support the development of natural alternatives, in accordance with herbal-based prevention efforts that are increasingly in demand by the community.

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INTRODUCTION

Disease degenerative (genetic) which means existence decline progressive from efficiency an organ or increasing changes become bad with lost functions and changes chemistry in network (Kholisa et al., 2018). Disease degenerative or disease No infectious become problem health the

forefront that has not yet under control moment this is what causes death the highest in the world at 71%. Disease degenerative happen consequence a number of factor associated risks direct with inflammation, one of them pattern life that is not good. Inflammation this happen consequence from reaction oxidation excess that produces compound radical free and if the situation excessive in body will causes correlated oxidative stress strong with its emergence inflammation. Disease related degenerative with inflammation like disease heart coronary heart disease (CHD) and diabetes. Death The consequences of CHD in the world in 2019 were reported occurred in 17.9 million soul with criteria namely age not enough more from 70 years and 1.5 million soul death caused by consequence diabetes. Indonesia has a total prevalence of CHD and stroke of 13.6% and is the country with the highest prevalence of CHD and stroke. amount most diabetes sufferers in this world namely in 4th position, namely amounting to 8.4 million soul (Medyati, et al. 2018).

Disease degenerative that appears consequence pattern eating food Ready serving or instant as well as style less life activity be one of trigger main emergence disease degenerative which includes diabetes, osteoporosis, cancer, and disease cardiovascular. Until moment This disease degenerative has become reason death the largest in the world. Nearly 17 million more people died every beginning year consequence global epidemic of disease degenerative, in Indonesia disease degenerative like hypertension, diabetes mellitus, stroke, heart failure kidney chronicle show the number increased in 2018 from 2013 (Ministry of Health of the Republic of Indonesia, 2013).

Survey data *The Sample Registration System* (SRS) in Indonesia in 2014 stated that prevalence heart coronary by 1.5% in Indonesia and 1.6% in West Java. The high number death caused disease heart coronary due to factor external and internal. Internal factors such as genetics, smoking, lifestyle life, pattern eat something that is not healthy, activity physical deficiencies, stress levels, hypertension, and disorders emotional. While factor external like environment and lack of support family (Nafisah et al., 2024).

According to data (WHO) it states that disease heart coronary be one of problem health in system cardiovascular disease in number increase fast with number 6.7 million deaths cases (WHO, 2019). The World Health Organization stated that cigarette cause around 7 million death every year. This is predicted will experience improvement up to 8 million death every year in 2030. More of 6 million people died as smokers active and about 890,000 others die consequence caught exposure to cigarette smoke or known as smokers passive, as much as 80% of 1.1 billion smokers around the world come from from high-income countries low and medium (WHO, 2018).

There are various type disease heart that is disease heart coronary heart disease cerebrovascular, hypertension, disease arteries peripheral, disease heart rheumatism, disease heart default and fail heart disease heart is matter main cause death, will but No means No can avoided or treated. As for the medicine for the disease heart only For reduce or Relieves heart pain. Data from Mitra Medika Bondowoso Hospital period March 2021 the most used For disease heart is drug *Clopidogrel* with a total amount of usage 4,231 tablets of *Clopidogrel* is antiplatelet drugs that are pharmacological similar with ticlopidine. This drug can hinder freezing blood that results in a number of fatal condition to health humans. *Clopidogrel* metabolized by CYP450 enzymes so that produce metabolit active that can hinder aggregation platelets or pieces blood (platelets) stick in body (Rahasti et al, 2021).

There is a connection disease heart coronary with factor risk and with disease comorbidities, such as diabetes mellitus, hypertension and hyperglycemia cause the complex therapy that will (Nadhira et al., 2022). Pharmacology is the science that studies drugs, particularly those related to the effects of their physical-chemical properties on the body, and the response of body parts to drug properties. Selection type drug will greatly affect quality use drug in election therapy.

Nowadays, many choice drug so that need careful consideration in choose therapy in accordance with disease. Various drugs synthetic contain antioxidants among them Contains

vitamin C & NAC (*N- Acetylcysteine*). Antioxidants have very easy nature oxidized, so that radical free will oxidize antioxidant and protect molecule other in the cell from damage consequence oxidation by radicals free or oxygen reactive (Werdhasari, 2014).

Treatment is divided into two types: modern medicine and traditional medicine. Modern medicine uses chemical-based medications that have undergone clinical trials. Traditional medicine, on the other hand, utilizes natural herbal ingredients, such as fruits or plants, traditionally believed to treat a particular disease. Heart disease can be treated with traditional medicine using red pomegranates, which contain secondary metabolites to protect the heart and prevent blockages in blood vessels (Hayun & Karina, 2016).

Plants are a source of natural exogenous antioxidants. These natural antioxidants are found in plants, namely polyphenol compounds, carotenoids, and vitamins. Antioxidants have pharmacological effects such as anticancer, anti-inflammatory, antibacterial, and antiviral (Zuraida, 2017). The pomegranate plant is a deciduous shrub with a curved shape and many branches, and also has a height of 5-18 m. Pomegranates contain flavonoid compounds with anti-carcinogenic substances that act as antioxidants that have benefits in preventing free radicals in the body, repairing damaged body cells, and providing protection against skin cancer, heart disease, and cholesterol (Caruso et al, 2020). Red pomegranate (*P unica granatum* L.) is rich in secondary metabolites such as *Quercetin, Ellagic acid, caffeic acid* and *phenol*. The high concentration of diverse secondary metabolites in this fruit allows it to treat and protect the heart. To observe the response of these metabolite compounds to heart disease, the reaction can be observed using *Molecular Biology. docking.*

Docking molecular is one of the tools in structural molecular biology for designing drugs with computers. Computational or molecular - *based studies Docking* is a screening method to find active compounds with pharmaceutical potential from plants (De Ruyck et al., 2016). And the purpose of ligand-protein docking is to understand and predict molecular recognition, find possible binding modes and predict binding affinity. *Molecular studies Docking* can help in studying drugs, ligands and receptor interactions as well as proteins by computing biological data to predict how a drug molecule will interact with its biological target at the molecular level (Pratama, 2016).

The aim of this study was to determine the active compounds contained in the red pomegranate plant (*Punica granatum* L.), especially Quercetin, Ellagic acid, caffeic acid, and Phenol, which are suspected to have potential as heart disease inhibitor agents through *molecular testing. docking*. In addition, this study also aims to evaluate the effectiveness of these compounds in inhibiting the development of heart disease, so it is hoped that it can provide scientific contributions in the development of natural products as potential therapeutic agents.

With background behind This writer interested For do study about "*Molecular docking* test on plants fruit pomegranate red (*Punica granatum* L.) as disease inhibitor agent heart (cardiovascular)" study This For see potential compounds found in fruit pomegranate red that may can protect or hinder emergence disease genetics heart with method *molecular docking* and can see interaction between target proteins and potential compounds in treat disease heart.

RESEARCH METHOD

This research was conducted from March 26 to April 10, 2025, at the Biology Laboratory of the State Islamic University of North Sumatra, Medan. This in silico study focused on molecular analysis. docking to identify the potential active compounds from red pomegranate (*Punica granatum* L.) as a heart disease inhibitor agent. The tools used in the study included an Asus BR1100CKA laptop with Intel Celeron N4020 CPU specifications, 4GB RAM, 128GB Nvme SSD, and a Windows 10 Pro operating system. Various software used included PubChem, PASS Online, Swiss Target Prediction, STRING -db, NCBI, SwissModel, PyMol, PyRx, ProTox, and Protein Plus, all of which ran on a 64-bit system and were connected to the Axis internet network.

The ingredients used consist of a 3D structure of active compounds from red pomegranate extract, namely Quercetin, Ellagic acid, caffeic acid, and Phenol. As a comparison, one active drug compound, Clopidogrel, was added. The ligand structure was obtained through the PubChem website, while the macromolecular structure of the target protein was obtained from Swiss Target Prediction. The work procedure begins with searching and preparing the 3D structure of the active compound through PubChem in *sdf format* which is then further analyzed in PASS Online to determine the potential biological activity against a particular target. The probability values of Pa (probability of being active) and Pi (probability of being inactive) are observed to assess how much influence the compound has on the biological target.

Next, the target protein that plays a role in the mechanism of heart disease was identified through Swiss Target Prediction by selecting the Homo sapiens organism, and the results of the target protein were analyzed using STRING- db to ensure its association with the disease pathway based on KEGG Pathways. After the target protein was obtained, 3D structure validation was carried out by searching data in NCBI and downloading sequences at *the sequence level.* high *identity in FASTA format. The 3D structure of the target protein is also downloaded in PDB format for later use in the* docking process.

Preparation was performed using PyMol and PyRx software. Ligands downloaded from PubChem were saved in *pdb format*, then optimized by adding hydrogen and converted to *pdbqt format*. Meanwhile, the downloaded target protein was prepared by removing water molecules and making it a nonpolar molecule for more accurate docking. Docking analysis was performed using PyRx with the Vina Wizard feature. The prepared ligands and proteins were entered and docked to see the strength of the ligand interaction with the target protein based on the binding value. affinity. The interaction results were then visualized using PyMol, and further analyzed using Protein Plus to evaluate the success of ligand binding to the target protein.

The final stage of the research was ADME (Absorption, Distribution, Metabolism, and Excretion) analysis and compound toxicity using the SwissADME and ProTox websites. This analysis aimed to assess the suitability of the compound as a drug candidate by considering its pharmacokinetic properties and potential side effects. The toxicity prediction process was carried out by incorporating *canonical The compounds were added* to the ProTox page and the LD50 values were observed, which were then categorized into six toxicity classes, from highly toxic to non-toxic. All data from the molecular results docking is then analyzed based on the *binding value affinity*, RMSD (Root Mean Square Deviation), and is associated with the Lipinski rule (Rule of Five) to evaluate the potential of compounds as drugs qualitatively and quantitatively based on the molecular interactions that occur.

RESULTS AND DISCUSSIONS

Target Protein Energy Value

a. *Quercetin, d*ata results from testing mark energy target protein binding to the compound *Quercetin* is:

Table 1. Energy results aldo-keto reductase family 1 member b target protein binding

Ligand	Binding Affinity	RMSD/ lb	RMSD/ ub
AKR1B1_1	-8.7	0.0	0.0
AKR1B1_2	-8.4	2,071	3,869
AKR1B1_3	-7.3	3,564	7,331
AKR1B1_4	-7.2	3,655	6,055
AKR1B1_5	-7.0	16,795	19,136
AKR1B1_6	-7.0	4,382	7,348
AKR1B1_7	-6.9	16,124	18.66
AKR1B1_8	-6.8	4,587	6.73
AKR1B1_9	-6.7	17,952	20,327

Based on analysis test results mark energy Aldo-Keto Reductase Family 1 Member B target protein binding on compounds *Quercetin* shows that Binding Affinity values are found at -8.7 to -6.7 kcal/mol. Negative values show that interaction between compound *Quercetin* with target protein is stable or safe. The value of -8.7 kcal/mol indicates the strongest interaction, while -6.7 kcal/mol indicates more interaction weak. At the point mark energy bond -8.7 kcal/mol, RMSD at lower and upper with the number 0.0 indicates that the ligand is in position stable and not experience change position. The RMSD value continues increase show that the ligand position becomes more No stable. For example, at -7.0 kcal/mol with The RMSD value of the lower bound reached 16.795 Å and the upper bound value was 19.136 Å, which indicates change relevant ligand positions from position initially. Energy value more bonds negative show more interaction stable, while increasing RMSD value show instability ligand position. Therefore that, compound *Quercetin* which has energy bond the lowest at (-8.7 kcal/mol) and the lowest RMSD (0) Å is the best in matter stability interaction with the target protein being AKR1B1_Quercetin1.

b. *Caffeic acid,* data results from testing mark energy target protein binding to the compound *Quercetin* is:

Table 2. Result data energy aldo-keto reductase family 1 member b target protein binding

Ligand	Binding Affinity	RMSD/ lb	RMSD/ ub
AKR1B1_1	-8.2	0.0	0.0
AKR1B1_2	-8.1	3,256	4.94
AKR1B1_3	-7.8	1,343	5,984
AKR1B1_4	-7.2	1,325	2.36
AKR1B1_5	-7.0	2,086	2,751
AKR1B1_6	-6.7	8,056	9,654
AKR1B1_7	-6.5	7,537	10,257
AKR1B1_8	-6.5	2,708	6,035
AKR1B1_9	-6.2	3,396	6,118

Based on results testing mark energy Aldo-Keto target protein bond Reductase Family 1 Member B on compounds *Caffeic acid* shows that Binding Affinity values are found at -8.2 to -6.2 kcal/mol. Negative values show that interaction between compound *Caffeic acid* with target protein is stable or safe. The value of -8.2 kcal/mol indicates the strongest interaction, while -6.2 kcal/mol indicates more interaction weak. At the point mark energy bond -8.2 kcal/mol, RMSD at the lower and upper with the number 0.0 indicates that the ligand is in position stable and not experience change position. The RMSD value continues increase show that the ligand position becomes more No stable. For example, at -7.0 kcal/mol with The RMSD value of the lower bound reached 2.086 Å and the upper bound value was 2.751 Å, which indicates change relevant ligand positions from position initially. Energy value more bonds negative show more interaction stable, while increasing RMSD value show instability ligand position. Therefore that, compound *Quercetin* which has energy bond the lowest at (-8.2 kcal/mol) and the lowest RMSD (0) Å is the best in matter stability interaction with the target protein AKR1B1_1.

c. *Phenol,* data results from testing mark energy target protein binding to the compound *Phenol* is:

Table 3. Result data energy aldo-keto reductase family 1 member b target protein binding

Ligand	Binding Affinity	RMSD/ lb	RMSD/ ub
AKR1B1_1	-5.9	0.0	0.0
AKR1B1_2	-5.7	1,397	2,271
AKR1B1_3	-5.4	11,895	12,725
AKR1B1_4	-5.4	11,909	12,664
AKR1B1_5	-5.1	1,945	2,668
AKR1B1_6	-5.0	12,528	13,312

Ligand	Binding Affinity	RMSD/ lb	RMSD/ ub
AKR1B1_7	-4.8	7,537	8,435
AKR1B1_8	-4.6	13,315	14,039
AKR1B1_9	-4.5	15,923	16,924

Based on results testing mark energy Aldo-Keto Reductase Family 1 Member B target protein binding on compounds *Phenol* shows that Binding Affinity values are found at -5.9 to -4.5 kcal/mol. Negative values show that interaction between compound *Phenol* with target protein is stable or safe. The value of -5.9 kcal/mol indicates the strongest interaction, while -4.5 kcal/mol indicates more interaction weak. At the point mark energy bond -5.9 kcal/mol, RMSD at the lower and upper with the number 0.0 indicates that the ligand is in position stable and not experience change position. The RMSD value continues increase show that the ligand position becomes more No stable. For example at -5.1 kcal/mol with The RMSD value of the lower bound reached 1.945 Å and the upper bound value was 2.688 Å, which indicates change relevant ligand positions from position initially. Energy value more bonds negative show more interaction stable, while increasing RMSD value show instability ligand position. Therefore, that, compound *Quercetin* which has energy bond the lowest at (-5.9 kcal/mol) and the lowest RMSD (0) Å is the best in matter stability interaction with the target protein AKR1B1_1.

d. *Ellagic acid,* data results from testing mark energy target protein binding to the compound *Ellagic acid* that is:

Table 4. Result data energy aldo-keto reductase family 1 member b target protein binding

Ligand	Binding Affinity	RMSD/ lb	RMSD/ ub
AKR1B1_1	-7.8	0.0	0.0
AKR1B1_2	-7.5	0.689	6,217
AKR1B1_3	-7.4	1,115	3,695
AKR1B1_4	-7.4	1,271	4,439
AKR1B1_5	-7.3	1,276	4,377
AKR1B1_6	-7.0	18.82	21,711
AKR1B1_7	-7.0	16,972	17,807
AKR1B1_8	-6.9	16,963	18,306
AKR1B1_9	-6.9	18,851	19,772

Based on analysis test results mark energy Aldo-Keto Reductase Family 1 Member B target protein binding to the compound *Ellagic acid* shows that Binding Affinity values are found at -7.8 to -6.9 kcal/mol. Negative values show that interaction between compound *Ellagic acid* with target protein is stable or safe. The value of -7.8 kcal/mol indicates the strongest interaction, while -6.9 kcal/mol indicates more interaction weak. At the point mark energy bond -7.8 kcal/mol, RMSD at *lower* and *upper* with the number 0.0 indicates that the ligand is in position stable and not experience change position. The RMSD value continues increase show that the ligand position becomes more No stable. For example, at -7.3 kcal/mol with The RMSD value of the lower bound reached 1.517 Å and the upper bound value was 1.276 Å, which indicates change relevant ligand positions from position initially. Energy value more bonds negative show more interaction stable, while increasing RMSD value show instability ligand position. Therefore that, compound *Ellagic acid* which has energy bond the lowest at (-7.8 kcal/mol) and the lowest RMSD (0) Å is the best in matter stability interaction with the target protein AKR1B1_1.

e. Drug Feasibility Tests Based on *Lipinski (rule of five)*

Table 5. Results of feasibility test analysis drug based on rule *Lipinski (rule of five)*

Compound	Molecular weight <500 (g/mol)	H – bond acceptor <10	H-bond donors <5	LogP <5	Molar Refractivity
Quercetin	302.24	7	5	1.63	78.03
Ellagic acid	302.19	6	4	1.31	75.31
Caffeic acid	180.16	4	3	1.2	47.16

Compound	Molecular weight <500 (g/mol)	H – bond acceptor <10	H-bond donors <5	LogP <5	Molar Refractivity
Phenol	94.11	1	1	1.24	28.46
Clopidogrel	321.82	3	0	3.61	88.96

Lipinski (*rule of five*) or the rule of five is something knowledge in the field pharmacological For look for characteristic chemistry medicine. *Lipinski* is method experimental and computational For estimate solubility, permeability membrane, and properties in regulation development medicine. *Lipinski* is something rule practical For evaluate similarity medication and determine whether compound chemistry with activity pharmacological certain own characteristic physical and chemical that will make it active drug in body human. And after see activity pharmacological every type compound drug so done testing eligibility drug in accordance with rule *Lipinski* (Rokoski, 2019).

Based on feasibility test results drugs on the table obtained mark *Lipinski (rule of five)* on three appropriate compounds rules and not found violation that is: a) Compound *Quercetin* which has heavy molecule 302.24 g/mol, 5 H-bond donors and 1 H-bond *acceptor* totaling 7, the value LogP 1.63 with *molar reactivity* totaling 78.03; b) Compound *Ellagic acid* which has heavy molecule 302.19 g/mol, 4 H-bond donors and 4 H-bond *acceptors* totaling 6, value LogP 1.31 with *molar reactivity* totaling 75.31; c) *Caffeic* acid compounds have heavy molecule 180, 1.6 g/mol, 3 H-bond donors and 1 H-bond *acceptor* totaling 4, value LogP 1.2 with *molar reactivity* totaling 47.16.

Of the three compound This show that compound This own appropriate value with test results that have been done and not done found violation. Can be seen that compound This can bind and produce complex values and ties (Gukasyan et al., 2022).

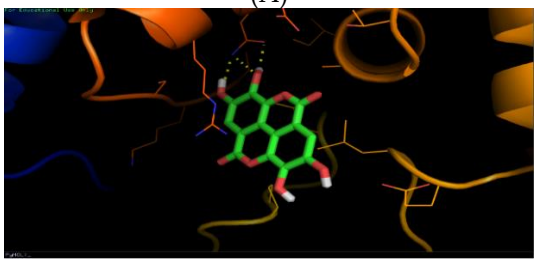
Based on these results, the compound *Quercetin* is in toxicity class 3 with LD50: 159mg/kg. This class is toxic if swallowed and is not included in the toxic category, making it possible to be used as a drug candidate. The *Ellagic acid compound* is in toxicity class 4 with LD50: 2991mg/kg. This class is toxic if swallowed and is not included in the toxic category, making it possible to be used as a drug candidate. *Caffeic acid compound* is in toxicity class 5 with LD50: 2980mg/kg. This class is toxic if swallowed and is not included in the toxic category, making it possible to be used as a drug candidate. *Phenol Compound* is in toxicity class 3 with an LD50 of 270 mg/kg. This class is toxic if swallowed and is not included in the toxic category, making it possible to be used as a drug candidate. Of the four compounds used, there are three compounds that can be drug candidates, namely *Quercetin*, *Ellagic acid*, and *caffeic AC ID*.

Parameters used to analyze *docking* results among them are (*Root Mean Square Deviation*) RMSD, the docking method is said to be valid if it has an RMSD value ≤ 2 Å (Muttaqin et al. , 2019). The RMSD value explains the deviation value of the error that occurs during *docking* . The smaller the RMSD value indicates that the deviation of the error in *docking* that's a little. The lower the free energy value of the bond, the more stable the ligand bond with the receptor will be (Pebriana et al , 2012).

Visualization of *Molecular Docking* Results

a. Visualization Results 3D structure between Ligand and compound *Ellagic acid*

(A)



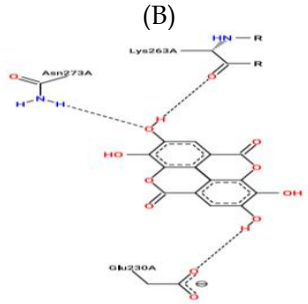


Figure 1. (A) Visualization 3D *molecular docking* structure of compounds *ellagic acid* which can bound with Aldo Keto Reductase Family 1 Member B protein, (B) Visualization 2D bond structure hydrogen and bonds hydrophobic bonding with Aldo Keto Reductase Family 1 Member B protein.

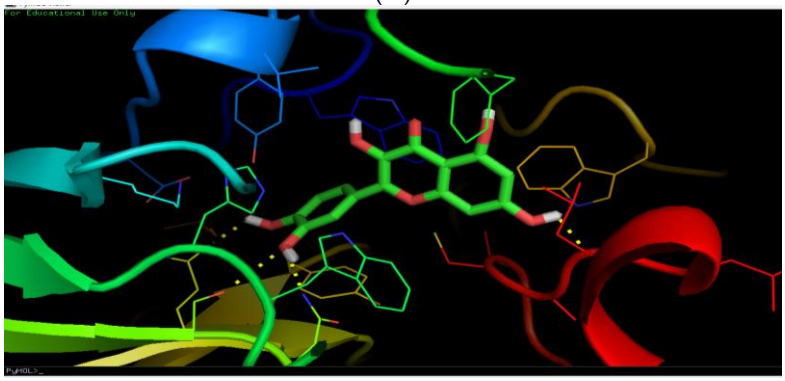
From the results visualization *docking* 3D structure is done with use *PyMOL software* For see data *scoring* results each ligand and protein that has been prepared whereas For visualization interaction bond 3D and 2D structures using *Protein Plus software*. From the results visualization 3D structure shows that the parameters of results first *docking* is energy affinity generated. From energy affinity can seen how much strong connected bonds between protein and ligand. Good affinity energy will produce increasing value negative that's the lowest. In value low affinity show that compound the need A little energy when in the binding process, so can it is said that energy low affinity prove that compound the own more potential big For can interact and form strong bond with the target protein. At the value constant inhibition (ki) is present the required concentration of ligand in inhibits target protein. Constant value good *inhibition* in the form of increasing value (ki) small. Stability ligand- receptor interactions compared straight with potential binding compounds, and can it is said that something target protein binding can predict ability *inhibition* from something compounds that can hinder something disease to the protein to which it binds. So, rate from energy Aldo keto reductase family 1 member B protein affinity in plants fruit pomegranate red own range from -7.8 to -6.9 kcal/mol whereas, energy bond ligand- free validation that is of -7.3 kcal/mol.

Mooring molecule used For know ligand interactions with macromolecules Because ability For predict with level accuracy height and conformation of the ligand in the appropriate target binding site. Selection of the target protein used namely liver CYP450 enzymes man with CYP450 codes available in the protein data bank (rscb.pdb). Ligands (compounds) can interact with energy the smallest bond so that part molecule be in a state stable (Abdelmonem et al., 2024). From the results visualization 2D structure visible that the ligand binds something bond hydrogen and bonds hydrophobic. When the compound *Ellagic acid* interacts with nonpolar ligands will happen change water molecules that surround the ligand and can cause improvement stability complex through interaction hydrophobic. Energy value positive hydrophobic show that interaction This can profitable in a way affinity, because reduce entropy system with minimize interaction with water. In the compound *Ellagic acid* group hydroxyl can act as a bond donor hydrogen present in the ligand. Interaction This No only increase stability the complex formed but also contributes to affinity binding between *Ellagic acid and ligands.* Bond energy strong and specific hydrogen strong and specific For increase potential of ellagic acid as a ligand in system biological.

Based on RMSD value which shows that compound *Ellagic acid* has energy bond lowest (-7.8 kcal/mol) and lowest RMSD (0) Å, and can seen this is what can it is said Good in matter stability interaction between protein targets. This is can confirmed that compound *ellagic acid* own potential and can made as candidate something drug as inhibitor in disease genetics heart.

b. Visualization 3D structure between Ligand and compound *Quercetin*

(A)



(B)

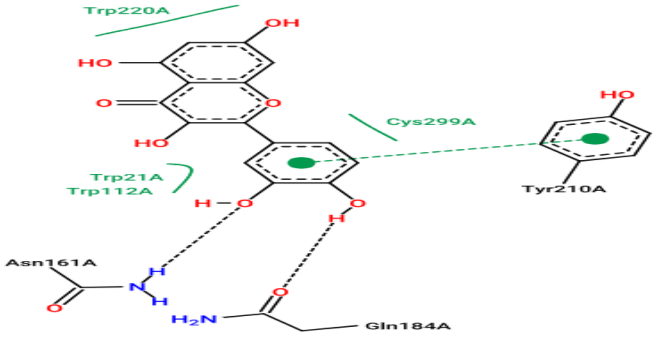


Figure 2. (A) Visualization 3d *molecular docking* structure of compounds *quercetin* which can bound with aldo keto reductase family 1 member b protein, (b) visualization 2d bond structure hydrogen and bonds hydrophobic bonding with aldo keto reductase family 1 member b protein

Docking visualization results using PyMOL and Protein Plus show that Quercetin compound from fruit pomegranate red (*Punica granatum* L.) has potential as an inhibitor of the target protein Aldo Keto Reductase Family 1 Member B (AKR1B1), with The binding affinity value is -8.7 kcal/mol and RMSD is 0.8 Å which indicates stability and validity bond. Quercetin fulfills Lipinski criteria (Rule of Five), without violations, which indicate potential activity good pharmacology. The interactions formed covering bond hydrogen and hydrophobic with a number of residue amino acids, which play a role role important in activity biological Quercetin such as antioxidant, anti-inflammatory, and inhibitory enzymes. Combination energy bond This strengthen potential of Quercetin as candidate agent therapeutic disease heart.

CONCLUSION

Based on the results of the research that has been carried out, it can be concluded that the red pomegranate plant (*Punica granatum* L.) contains four main active compounds, namely Ellagic acid, caffeic acid, Quercetin, and Phenol, which have potential as inhibitory agents for genetic heart disease based on molecular analysis docking. The four compounds showed positive interactions with the target proteins, with Ellagic acid and Quercetin displayed the most stable bonds and binding values the lowest affinity values were -7.8 kcal /mol and -8.7 kcal /mol, respectively, and the RMSD value was 0 Å. Both also met the toxicity parameters, where Ellagic Acid is included in class 4 and Quercetin in class 3, which indicates a relatively good level of safety. Visualization of the 3D structures of these two compounds shows the presence of hydrogen bonds and interactions

with amino acids in the target protein Aldo Keto. Reductase Family 1 Member B (AKR1B1), which shows strong potential as a drug candidate for genetic heart disease.

As a follow-up, it is recommended that further research be conducted using molecular testing. docking on other receptors to broaden the understanding of the mechanism of Ellagic compounds acid and quercetin in inhibiting genetic diseases, particularly those related to the heart. Given that this study is in silico and only provides a predictive picture, further validation through *in vitro* and *in vivo tests* of the four active compounds is needed to ensure efficacy and safety in a more realistic biological context. This experimental approach is expected to strengthen scientific evidence and support the development of red pomegranate plants as a natural source of potential drugs for the treatment of heart disease.

In silico prediction validation must be conducted through in vitro testing on cells related to antioxidant and anti-inflammatory mechanisms, followed by in vivo testing on degenerative cardiovascular animal models to assess efficacy, toxicity, and metabolic interactions, and concluded with controlled clinical trials to ensure safety, efficacy, and optimal dosage in humans. The findings of this research contribute to global efforts in the development of natural therapies for degenerative diseases, particularly cardiovascular diseases, by accelerating the discovery of drug candidates based on natural compounds, reducing research costs, and promoting integration between bioinformatics, ethnopharmacology, and clinical research to support complementary and integrative medicine.

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