EVALUATION OF PHYSICOCHEMICAL AND BIOACTIVE TOXICITY FROM MANGO SEED AS A STUDY IN SEARCHING NEW DRUG FOR ACNE IN SILICO

Azis Mawardi[1], Rossa Martha Wulandari[1], Thiya Fathiyatul Fauziah[1], Nabilah Miftachul Khoiriyah[2], Moch. Mustakim[1], Vina Fitria Wulandari[1], Nurul Jadid Mubarakati[1]

[1]Departments of Biology, Faculty of Mathematics and Natural Science, University of Islam Malang, [2]Departments Agribusiness, Faculty of Agriculture, University of Islam Malang
*Corresponding author: nurul.jadid@unisma.ac.id

Abstract

The objective of this study was to evaluate physicochemical and toxicity of bioactive compounds from mango seed with aldo-keto reductase family 1 receptor (PDB ID : 4DBS) and Catechol-O-Methyltransferase receptor (PDB ID : 3BWM). Identification of physicochemical's characteristic refers to the Lipinski's rule, whereas toxicity analysis was used pkCSM Online Tool. The interaction of bioactive compounds with macromolecule was examined via a molecular-specific docking analysis. The results showed that the twelve compound's test from mango seeds complied with Lipinski's rule with 83% according to the criteria for drug candidates. The ADME analysis also revealed that the Hydroxybenzoic acid did not violate any of the Lipinski's rule and had high gastrointestinal absorption. Generally, the toxicity and molecular docking analysis showed the compounds inhibited the cathecomaline macromolecule with a series of Quercetin>Quercitrin>Caffeic acid>Rutin. Therefore, the mango seed can be recommended for futher development as an acne drug candidate.

Keyword: acne, in silico anlysis, mango seed, Lipinski's rule, toxicity

Looks are very important to a person. A common occurrence is in the skin like acne. Pimples are a common disease. However, the vast majority of people in general feel strongly avoided and threatened by the disease. Especially in women who feel a decrease in confidence when they are developing acne. Acne is a skin disorder caused by excess oil content of the skin. The oil will clog up and cause an inflammation of the hair follicles that will cause skin cells to die. Acne generally develops on the body parts with a high oil content such as the face, the neck, the upper torso, and the back (Fadli, 2021).

The appearance of acne is also due to the support of bacteria that cause acne. *Propionibacterium acnes* and *Staphylococcus epidermis* are bacteria that are reported to be the bacteria that causes acne (Zahrah, Mustika, & Debora, 2018). *Propionibacterium acnes* is a positive gram bacterium that forms skin pimples. Presentation of an antibacterial agent can be the development inhibitor of the *Propionibacterium acnes* bacteria so that the acnes surface can be minimized. One natural adaptive bacterium of acnes bacterium is by using phenolic compounds found in plants such as the one contained in the mango nut.

The mango plant (*Mangifera indica L.*) is common throughout the region of Indonesia. The ease with which surgical techniques, the speed at reproduction, the climate and the good weather and the high prospects for benefits from the cultivation of mangoes are one of the reasons for finding mangoes and mangoes in Indonesia. Many of these plants are yearly, producing plants. When the season of mango harvest arrives, people's consumption rate of mango fruit will increase. The sweet - sour fruit is commonly consumed only by the pulp of the fruit and the mango seed is thrown away.

The unused mango seeds, in turn, accumulate into an ecological waste of mango seeds. Therefore, use of the mango waste is required. One is to make good use of the presence of bioactive compounds found in mango fruit seeds. It is known that the seeds of mango fruit are a good source for such things as Kampesterol, β-sitosterol, Stigmasterol, Tokoferol, Polyphenols, and Tannins and mango seeds in particular have a high level of phenolic content (Zulhipri, 2016).

As in barlow's research, (2004) it was found that inside mango seeds there is an extremely high level of phenolic compounds. Moreover, in the extract of mango fruit tannins, flavonoid, terpenoid, saponin (Laoi, Lukstyowati, & Syawal, 2020) and alkaloid (Prihandani, Noor, Andriani, & Poeloengan, 2016). Judging from the compound's properties it is known that mango seeds are full of antioxidants and antibacterial.

Another study reported that mango fruity extract has a high level of antibacterial against bacteria propionibacterium acnes as one of the bacteria that supports the formation of acne (Munawwarah, Aufia, & Masitha, 2017). Such antibacterial content may be an alternative to the natural prevention of acne. Thus further developments are needed for the effect of the phenolic compounds on the mango fruits as agents of the antibacterial bacteria inhibitors of the *Propionibacterium acnes*.

Virtual research at this time is still scarce. Virtual research conducted is intended to reduce the potential for clinical trials as they do in most studies. Furthermore, research is conducted *in silico*, which means it is done using existing software to determine the interaction between drugs and pathogens in the body.

Based on the above problems, the purpose of this study is to analyze the physiological properties and the toxicity of active compounds on mango seeds for catecholamine *in silico*.

Methods

The study uses virtual screening approaches through *in silico* exploration of mango seed potential as well as molecular docking analysis. Molecular docking analysis is directed to look at bonded energy between *Catecholamine* and phenolic seed compounds. Parameters used are the value of the drug criteria based on the rules of lipinski, ADMET, Root Mean Square Diviation (MSD) and binding affinity.

As for the procedure in this research, it is as follows:

A. Analysis Of Physicochmical and Toxicity Of Active Compounds

   The physicochemical identification of the compound active seeds are identified by researches at http://www.scfbioiitd.res.in/software/drugdesign/lipinski.jsp (lipinski database rules) and pkCSM online tool programs are known for ADME and Toxicity analysis (http://biosig.unimelb.edu.au/pkcsm/prediction) by insertion SMILES each active compound.

B. Analysis of Molecular Docking

   In the molecular docking phase aims to predict active compound interactions of catecholamine enzymes on acne.

Prepare Ligan

The study used ligan's recovered from pubchem's webserver, which was next analyzed by the protein of his target using the Web Server Stitch Database. Based on the search ligan on the web found four active compounds closely related to *Catecholamine* (Table 1).

Table 1. Prepare Ligan

No	Active Compounds of Mango Seeds	
	Before Analysis stitch database	After Analysis stitch database
1	*Rutin* (CID:5280805), penta-O-galloyl-beta-D-glucose (CID: 117064545), Gallotannin (CID : 12795683), *Vanillic Acid* (CID : 1183),, *Hydroxybenzoic Acid* (CID : 135), *Gallic Acid* (CID:370), *Catechin* (CID:1203), *Chlorogenic Acid* (CID:1794427), *Caffeic Acid* (CID:689043), *Ellagic Acid* (CID:5281855), *Quercitrin* (CID:5280459), *Quercetin* (CID:5280343), *Kaempferol* (CID : 5280863).	Rutin (CID : 5280805), *Quercitrin* (CID:5280459), *Quersetin* (CID : 5280343), *Caffeic Acid* (CID:689043),*S-Adenosylmethionine* (SAM) (CID : 34755), *Nicotinamide-Adenine-Dinucleotide Phosphate* (NADP) (CID : 5885)
	Total test compounds = 13 compounds	Total test compounds = 4 compounds and 2 *native ligand* (SAM and NADP)

Protein Receptor Preparation. The molecular structure of the receptors used is akr1c3 (*Aldo-keto reductase family 1 member C3*) GDP id: 4DBS and COMT (*Catechol-O-Methyltransferase*) GDP id: 3BWM can be downloaded using the web server RCSB PDB (rcshttpswww.rcs://org). Preparations are made by removing unneeded ligan, chain, and water molecules then stored in pdb format.

The Molecular Docking Stage. Based on the stitch search database found four active compounds on mango seeds that are closely related to target proteins that are then continued to the moleculer docking phase of analysis. Ligation-target docking computations are implemented to analyze the Catecholamine complex structure as a target, molecular docking analysis is run using The Biovia Discovery STUDIO under PyRx software. The docking analysis shows binding affinity and interaction to ligan's receptors. The first thing to do is to input the target protein (receptors) and ligan who have been in the preparation of the application. Next, after target proteins and ligan's input then proceed with Grid box settings. Then comes molecular docking. Molecular docking are then stored in PDBQT format to continue at the next stage.

The Validation And Visualize Docking Results. Validation and visualization of molecular docking interactions using the Discovery Studio Virtualizer software. To see the interactions generated by molecular docking, further visualization, 2d and 3d were used for the Discovery Studio Virtualizer software. Visualize results can show the interaction of amino acids in the form of 2 dimensions and 3 dimensions. Further on the interactions were analyzed the links forming between the receptors and ligan.

The results of this study take secondary data from databases that are then systematically collated into tables and pictures by reading data based on the physicochemical properties, admet, RMSD values, binding affinity and amino interactions.

Finding and Discussion

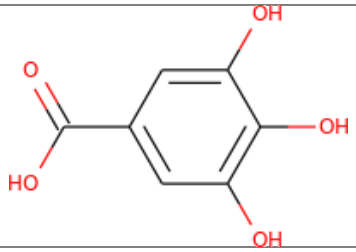
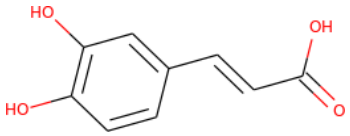
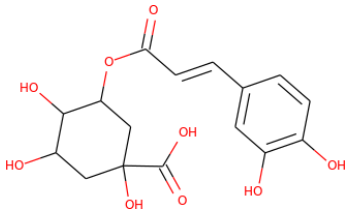
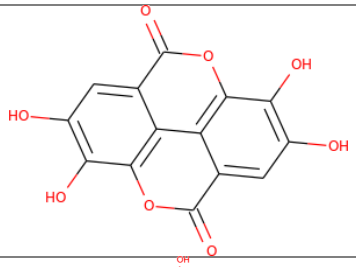
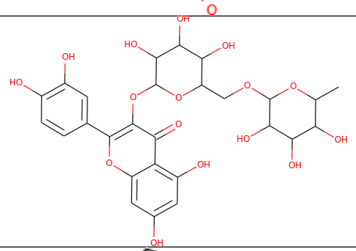
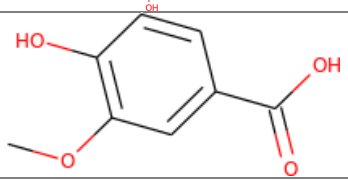
Acne is a chronic inflammatory disease of the cystic units marked by comedo, papula, nodul, cyst, and scar. Indeed, acne does not cause serious problems, but it does affect psychologically such as a loss of confidence. Factors that can cause such acne as genetic, endocrine, stress, bacteria, and several other factors (Meilina & Hasanah, 2018). Some bacteria that can cause pimms are bacteria like co-bacterium acnes (Daughter, etc., 2019), staphylococcus epidermis, and staphylococcus aureus (Ardhany, et al., 2019). One way a pimple treatment is to suppress the growth of the bacteria that causes it by suppressing acnes

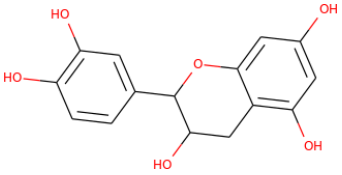
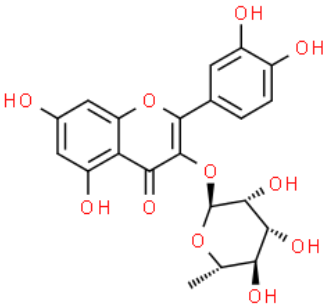
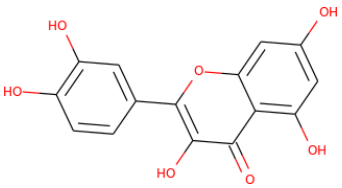
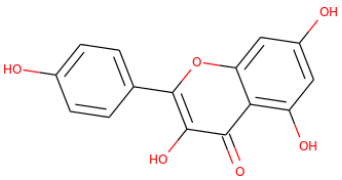
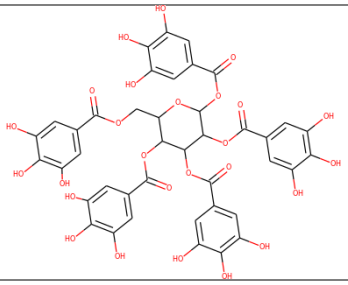
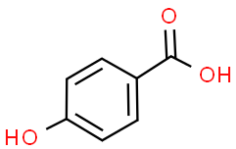
bacteria by giving natural antibacterial agents like the phenolic compounds (Aritonang, et al., 2013).

Some studies have proved that mango seeds are a rich source of different phenolic and antioxidal compounds (Lim, et al., 2019). In addition, mango seeds can be used as bacterials because they have high levels of phytochemical, alkaloids, flavonoid, and saponin. An alkaloid compound in mango seeds is reported to have activity as antibacterial, while tannins compounds are reported to have protective mucosa to prevent bacterial infections, which can also increase intestinal permeability (Munawwarah, et al. 2017)

The analysis used in the study is that of lipinski and admet. This analysis was carried out to determine the active compounds that could be used as drug candidates for further clinical trials (Table 2)

Table 2. Lipinski from Mango Seed Active Compounds

No	Active Compounds	molecular formula	Structure 2D	Lipinski's Rule	
				Criteria	Score
1.	*Gallic Acid*	$C_7H_6O_2$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	170 0.50 5 4 38
2.	*Caffeic Acid*	$C_9H_8O_4$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	180 1.19 4 3 46
3.	*Chlorogenic Acid*	$C_{16}H_{18}O_9$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	354 -0.64 9 6 82
4.	*Ellagic Acid*	$C_{14}H_6O_8$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	302 1.24 8 4 68
5.	*Rutin*	$C_{27}H_{30}O_{16}$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	610 -1.87 16 10 137
6.	*Vanillic Acid*	$C_8H_8O_4$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors*	168 1.09 4 2 42

				Molecular refractivity	
7.	*Catechin*	$C_{15}H_{14}O_6$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	290 1.54 6 5 73
8.	*Quercitrin*	$C_{21}H_{20}O_{11}$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	448 0.29 11 7 105
9.	*Quercetin*	$C_{15}H_{10}O_7$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	302 2.01 7 5 74
10.	*Kaempferol*	$C_{15}H_{10}O_6$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	286 2.30 6 4 72
11.	*Penta-O-galloyl-beta-d-glucose hydrate*	$C_{41}H_{32}O_{26}$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	940 1.68 26 15 209
12.	*Hydroxybenzoic Acid*	$C_7H_6O_3$		Molecular weight (kDa) *Log-P* *H-bond acceptors* *H-bond donors* *Molecular refractivity*	138 1.09 3 2 35

On lipinski's analysis the value of an active molecule of the substance is no more than 500 because a substance that has a smaller molecular weight would be easier to penetrate a biological membraner (Adriani, 2018), the value of a Log P no more than 5, the value of H donors is no more than 5, the value of H acceptor is no more than 10, teh value of molar refractifity between 30-140, if 3 of the 5 criteria meet, it fulfills the rule of lipinski

(Lipinski, 2004). Based on the results of lipinski's analysis, it shows the table-1 that there are 10 active compounds that meet lipinski's rule *Gallic acid, Caffeic acid, Chlorogenic acid, Ellagic acid, Vanillic acid, Cathecin, Quercitrin, Quercetin, Kaempferol* dan *Hydroxybenzoic acid*. While the active compounds *Rutin* and *Penta-O gallyoyl-beta-d-glucose hydrate* unqualified lipinski's rules. 83.3% of the active compounds tested qualified lipinski's rules, while 17.7% of the compounds tested unqualified lipinski's rules. This shows that 83.3% of the active compounds found in *Mangifera Indica* seeds can be used as a possible drug candidate. The molecules of active compounds that do not meet the rule of lipinski are recommended for injection and zopolrestat, and they are not recommended as being used orally (Suhadi, et al., 2019)

PkCSM *online tool* is used to test the properties of ADME and its toxicity. From data gained in absorpsi range between 36,377% - 83,961%, this shows that such active compounds have good absorpsi values, unless regular active compounds *Rutin* dan *Penta-O gallyoyl-beta-d-glucose hydrate* which has absorpsi value 0%, because absorpsi values are said to be good if absorpsi is >80% and if <30% is lost.

In order to predict the absorption of drugs given orally, permeability in single layers of $CaCO_2$ is often used as an in vitro model of the intestinal mucosa. The log-papp value range between (-2.23) -0.84 which shows low permeability in $CaCO_2$ cells, while the *Hyrobenzoic Acid* substance has Log-Papp 1.51 shows being good permeable because score more than 0.90.

VDSS represents a total dose of distributed volume that should be evenly distributed to provide the same concentration as on blood plasma. If log value VDSS > 0.45 active compounds have high distribution volume, -0.15 >VDSS< 0.45 moderate and low distribution volume if < -0.15. The active compounds *Chlorogenic acid, Rutin*, *Cathecin, Quercitrin, Quercetin, Kaempferol,* has VDSS values ranging from 0.4034722 to 1.663 so that the compounds have high distribution volumes, *Ellagic acid* and *Penta-O gallyoyl-beta-d-glucose hydrate* have VDSS values ranging from 0.2604167 to 0,008 so that they have moderate distribution volumes, while *Gallic acid, Caffeic acid, Vanillic acid,* dan *Hydroxybenzoic acid* has a VDSS score ranging from -1,855 to -1,098 so the compounds have low distribution volumes.

BBB (blood brain barrier) is the drug's ability to penetrate blood clots in order to dapay increases the properties of medications that have a pharmacological effect on the brain and to reduce the toxicological side effects. The compound will be able to penetrate Log BB > 0.3, and cannot be properly distributed when the Log BB < -1 (Pratiwi, et al., 2020). On active *Quercitrin* compound has the value of the Log BB 1,495 it shows quercitrin can penetrate blood and blood in the brain well because it has a Log BB >0.3 value. As for the *Chlorogenic acid, Rutin, Quercitrin, Quercetin, Kaempferol, Hydroxybenzoic acid, Gallic acid, Caffeic acid, Ellagic acid, Vanillic acid, Cathecin,* dan *Penta-O gallyoyl-beta-d-glucose hydrate* has a Log BB value between -525 and -0.334 suggests that the compounds have the ability to withstand too good brain blood.

The table can be seen that all active compounds neither suppress nor affect the enzyme CYP2D6, so it is possible to predict that the compound's turunana tends to be metabolized by the P450 enzymes that play an important role in detoxification of the body.

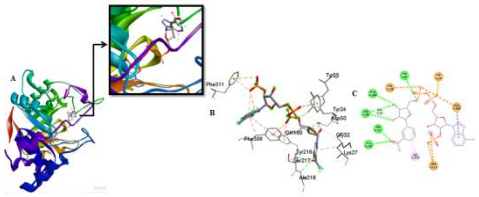
The *Renal OCT2 (Organic Cation Transporter) substrate* is a first step in the secretion of the renal organic gland, so it plays a significant role in determining the pharmacogenic properties of medicine (Wright, 2019). From a table it can be seen that 11 active compounds of mango beans do not affect OCT2 substrate, so the compound changes instead of OCT2 substrate, as OCT2 substrate has potential side effects when given along with OCT2 inhibitors. As for the filling of compound *Penta-O gallyoyl-beta-d-glucose*

hydrate affects OCT2 substrate, thus allowing derivative compound to become OCT2 substrate.

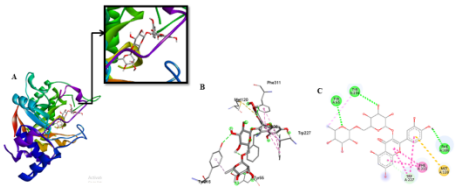
Cathecin compounds have a LD50 value of 10,000 kg/mol, they go into class 5 which means it has a low acute toxicity effect, whereas the *Quercitrin, sedangkan Kaempferol, Chlorogenic acid, Rutin, Hydroxybenzoic acid, Gallic acid, Caffeic acid, Ellagic acid, Vanillic acid,* dan *Penta-O gallyoyl-beta-d-glucose hydrate* has an LD50 grade ranging from 2000-5000 to grade 4 which means it has a small acute toxicity and *Quercetin* that has an LD50 value of 159 kg/mol to grade 3 which has a moderate acute toxicity effect. In the mutagenic Ames and toxicity tests of the liver, it shows all the active compounds tested that show no mutagen or toxicity in the liver.

At the level of the target protein analysis using the stitch database and string databases is found that Caffeic acid corresponds directly to the catecholamine receptors while some other substances such as *Rutin, Quercetin, Quercitrin* have a connection with *catecholamine* through another protein path of AKR1C3 (data not shown). Analysis has shown that other compounds have no direct or indirect connections to target proteins.

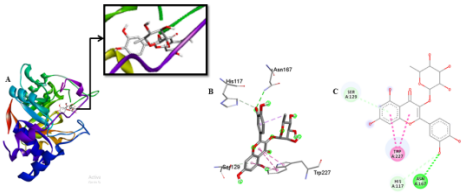
Molecular docking is a way of looking ata compound that produces biological effects when attached to the receptors (Asshiddiq, et al., (2021). Molecular docking is performed by mixing the most potential compounds derived from target protein analysis. Moleculer docking is engaged to learn the interactions produced between 4 active compounds on mango seeds and *Aldo-keto reductase family 1 member C3* (AKR1C3) and *Catechol-O-Methyltransferase* (COMT). *The molecular docking produces interactions demonstrated by the bond in amino acid residue.* The image results from the interaction of active compounds with AKR1C3 receptors and COMT can be seen in the following pictures:



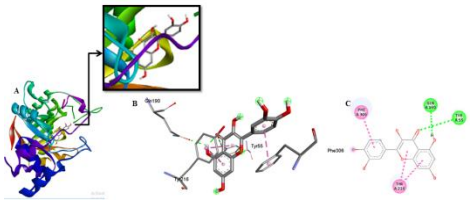
Gambar 1. (A) Moleculer docking protein simulation results AKR1C3 (PDB ID :4DBS) with NADP *Nicotinamide-Adenine-Dinucleotide Phosphate* (*Native Ligand* AKR1C3)*;* (a) Protein-ligan complex; (b) 3D structure interaction; dan (c) 2D structure interaction



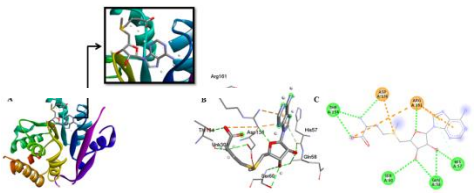
Gambar 2. (A) Moleculer docking protein simulation results AKR1C3 (PDB ID :4DBS) with *Rutin;* (a) Protein-ligan complex; (b) 3D structure interaction; dan (c) 2D structure interaction



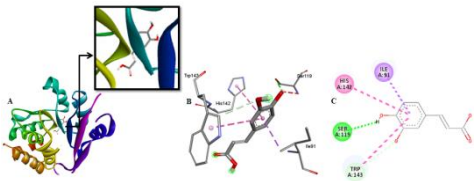
Gambar 3. (A) Moleculer docking protein simulation results AKR1C3 (PDB ID :4DBS) with *Quercitrin;* (a) Protein-ligan complex; (b) 3D structure interaction; dan (c) 2D structure interaction



Gambar 4. (A) Moleculer docking protein simulation results AKR1C3 (PDB ID :4DBS) with *Quercetin;* (a) Protein-ligan complex; (b) 3D structure interaction; dan (c) 2D structure interaction



Gambar 5. (A) Moleculer docking protein simulation results COMT (PDB ID :3BWM) with *S-Adenosylmethionine* (*Native Ligand* COMT)*;* (a) Protein-ligan complex; (b) 3D structure interaction; dan (c) 2D structure interaction



Gambar 6. (A) Moleculer docking protein simulation results COMT (PDB ID :3BWM) with *Caffeic acid*; (a) Protein-ligan complex; (b) 3D structure interaction; dan (c) 2D structure interaction

Molecular docking is obtained value bonding energy acquired between active compounds AKR1C3 and COMT receptors. In addition, molecular docking produces interactions of amino acid residue with various types of bonds. The result of the interaction of amino acid residue between the active compound and the target protein AKR1C3 and COMT can be seen at table 3.

Table 3. Results of Interaction of Amino Acid Residues with Proteins

No	Name of compound/ligan	Interaction Type		
		Protein TPH1		Protein GLI
1	Control / AKR1C3	Hydrogen bond : GLY22, ASP50, TYR55, GLN190, SER217, ALA218, PHE311 Hydrophobic bond: TYR24, TYR216, PHE306	Kontrol / COMT	Hydrogen bond: HIS57, GLN58, SER60, THR134, ASP 136,ARG161, UNK301, HIS57 Hydrophobic bond: ARG161
2	*Quercetin*	Hydrogen bond: TYR55, GLN190 Hydrophobic bond: TYR216, PHE306	*Caffeic acid*	Hydrogen bond: SER119, TRP143 Hydrophobic bond: LE91, HIS142, TRP143
3	*Quercitrin*	Hydrogen bond: HIS117, ASN167 Hydrophobic bond: SER129 TRP227		
4	*Rutin*	Hydrogen bond: TYR55, TYR216, PHE306 Hydrophobic bond: MET120, TRP227, PHE311		

There are 7 amino acid residues that are bound between the target protein AKR1C3 and Rutin, a bond formed in the form of a conventional hydrogen bond with amino acid TYR55, TYR216, PHE306. Pi- Sulfur bond with MET120, Pi- Donor hydrogen bond with TRP227, Pi- Pistacked bond with PHE311, Pi-Pi T-Shaped bond with PHE311. The affinity binding value obtained is -8.9 kcal/mol. *Quercitrin* is bound to 7 amino acid residues in the form of hydrogen carbon bonds with amino acids HIS117. Pi Hydrogen Donor bond with SER129, hydrogen conventional bond withASN167, Pi-Pi T-Shaped bond with TRP227. The affinity binding value obtained is -9,0 kkal/mol. *Quercetin* is bound to 4 amino acid residues in the form of hydrogen carbon bonds with amino acids TYR55, GLN190 dan ikatan Pi-Pi Stacked with TYR216, PHE306. The affinity binding value obtained is -9,4 kkal/mol.

In *Caffeic acid* compounds with COMT receptors produce 5 amino acid residues that are bound between the compound and the receptor. The bond is in the form of hyrogen cpnventional bond with amino acid SER119, Pi-Sigma bond with ILE91, Pi-Pi T-Shaped bond with HIS142 and TRP143 and hydrogen carbon bond with TRP143. The affinity binding value obtained is -6,7 kkal/mol.

Table 4. Recapitulation of physiological properties, toxicity and the value of bonding energy that's formed between the active compounds found in target protein analysis.

No	Compound	Lipinski	absorption	Distribution	Metabolism	Excretion	Toxicity class	Binding Affinity (kkal/mol)
1	*Caffeic acid*	Yes	No	No	Yes	Yes	4	-8.9
2	*Rutin*	No	No	No	Yes	Yes	5	-9.0
3	*Quercitrin*	Yes	No	Yes	Yes	Yes	4	-9.4
4	*Quercetin*	Yes	No	No	Yes	Yes	3	-6.7

Based on the physiological properties of toxicity, target protein analysis, and bond value *Quercetin* compounds are among the best active. This is because it meets the criteria for the physiological properties of toxicity and toxicity, the target protein analysis, and has the best binding bings of the *Quercitrin* and *Rutine* compounds of 99.4. But the *Quercetin* compound can't go beyond NADP as a native ligand in AKR1C3 protein. While on *Caffeic acid* compounds that interact directly with the catecholamine have already fulfilled in the physiological and toxicity qualities test, the target protein analysis, and has binding affinity that already exceed native ligand in the COMT protein, *S-Adenosylmethionine* -6.7 kkal/mol.

Conclusions and Suggestions

Based on the physiological and toxicity and molecular docking properties found that quercetin compounds are the best active compound for AKR1C3 receptors. This is because the compound meets all of the test criteria and has the highest binding affinity. Additionally, *Caffeic acid* compounds are the best for COMT receptors. Not only that, *Caffeic acid* compounds already meet in all test criteria beginning with the physiological properties test, toxicity, and molecular docking. This research needs to demonstrate the potential of mango seeds through a lab to know the effectiveness and efficacy of acne drugs.

Acknowledgements

Our most heartfelt thanks go to the Directorate General Of Learning And Ministry Of Education and Culture's Student Assistance for Funding Program Kreativitas Mahasiswa (PKM) in 2021. Thanks to the University of Islam Malang for its patronage. Not to be forgotten, we also thank protege Didik Huswo Utomo and Radita Pratiwi that have technically guided the workings of the methods *in silico* during the research.

References

Adriani. 2018. Prediksi Senyawa Bioaktif dari Tanaman Sanrego (Lunasia Amara Blanco) Sebagai Inhibitor Enzim Siklooksigenase-2 (COX-2) Melalui Pendekatan Molecular Docking. *Jurnal Ilmiah Pena*. 1(1):6-11.

Asshiddiq, R.F.I., Yahya, A. dan Risandiansyah, R., 2021. Potensi Antiadhesi Senyawa Aktif Hibiscus sabdariffa L Pada Penghambatan Protein Target IcsA Shigella flexneri Melalui Studi *in Silico Molecular Docking*. *Jurnal Kedokteran Komunitas*. 9(2):1-9.

Ardhany, S.D., dkk. 2019. Formulasi Sediaan Krim Anti Acne dan Uji Aktivitas Ekstrak Etanol Bawang Dayak (*Euleutrine bulbosa (Mill.) Urb*) Terhadap *Propionibacterium acnes*. *Jurnal Sains dan Kesehatan*. 2(2):121-126.

Aritonang, S. N., Nofita, T., 2013. Pengaruh Ekstrak Biji Mangga (*Mangifera indica*) Sebagai Antioksidan Terhadap Cita Rasa Dan Daya Simpan Bakso (The Effect of Mango Seed Extracts (*Mangifera indica*) as Antioxidant on The Flavor and Shelf Life of Meat Balls). *Jurnal Ilmu Ternak*. 13(2):22-26.

Fadli, R. 2021. *Jerawat*. URL : https://www.halodoc.com/kesehatan/jerawat.

Laoi, D., Lukstyowati, I., & Syawal, H. 2020. Pemanfaatan Ekstrak Etanol Biji Mangga Harumanis (*Mangifera indica L*) Untuk Menghambat Pertumbuhan Bakteri *Edwardiella tarda*. *Jurnal Ruaya*. 8(1):26.

Lim, K.J.A., Cabajar, A.A., Lobardio, C.F.Y., Taboada, E.B., dan Lacks, D.J. 2019. Extraction of bioactive compounds from mango (*Mangifera indica L.var. Carabao*) seed kernel with ethanol–water binary solvent systems. *J Food Sci Technol*. 1-9.

Lipinski C. 2004. *Lead and Drug Like Compounds* : The Rule Of Five Revolution. *Drug Discov*. 1(4):45-65.

Meilina, N. E., Hasanah, A. N. 2018. Review Artikel : Aktivitas Antibakteri Ekstrak Kulit Buah Manggis *(Garnicia mangostana L.)* terhadap Bakteri Penyebab Jerawat. *Farmaka*. 16 (2):322-328.

Munawwarah, Z. F., Aufia, W., & Masitha, N. 2017. Uji Aktivitas Antibakteri Ekstrak Etanol Biji Mangga (*Mangifera indica.L*) Terhadap *Propionibacterium acnes*. *Pharmasipha*, 1(1):31-35.

Pratiwi, R.I.A., Rahayu, T., dan Mubarakati, N.J. 2020. In Silico Screening of Schleichera oleosa Phytocompounds as Estrogen Receptors Alpha Inhibitors for Breast Cancer. *JSMARTech: Journal of Smart Bioprospecting and Technology*. 2(1):14-21.

Prihandani, dkk. 2016. Efektivitas Ekstrak Biji Mangga Harumanis terhadap *Staphylococcus aureus*, *Bacillus subtilis*, *Shigella sp.*, dan *Escherichia coli*. *Jurnal Veteriner*. 17(1):45-50.

Putri, dkk. 2019. Efektivitas Pemberian Salep Bonggol Pisang Ambon Terhadap Jerawat Pada Remaja. *Journal of Borneo Holistic Health*. 2(1):30-39.

Suhadi, Andrio, Rizarullah, dan Feriyani. 2019. Simulasi Docking Senyawa Aktif Daun Binahonh sebagai Inhibitor Enzyme *Aldose Reductase*. *SEL Jurnal Penelitian Kesehatan*, 6(2), 45-65.

Wright, S. H. 2019. Molecular and cellular physiology of organic cation transporter 2. *American Journal of Physiology - Renal Physiology*, *317*(6), 1669–1679.

Zahrah, H., Mustika, A., & Debora, K. 2018. Aktivitas Antibakteri Dan Perubahan Morfologi Dari *Propionibacterium acnes* Setelah Pemberian Ekstrak *Curcuma xanthorrhiza*. *Jurnal Biosains Pascasarjana*. 20(3):160-169.

Zulhipri. 2016. Ekstraksi Dan Karakterisasi Senyawa Metilgalatdari Biji Mangga Indramayu (*Mangifera indica. L*). *Proceeding of Mulawarman Pharmaceuticals Conferences*. 20-21 April 2016, Samarinda, Indonesia. 488-497.