SPIN
JURNAL KIMIA & PENDIDIKAN KIMIA
https://journal.uinmataram.ac.id/index.php/spin

INHIBITION MECHANISM OF COMPONENT EXTRACT OF BAWANG DAYAK ON DIABETES VIA MOLECULAR DOCKING STUDY

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DOI: 10.20414/spin.v5i2.8641

History Article
Accepted:
October 29, 2023
reviewed:
November 24, 2023
Published:
December 23, 2023

Keywords:
bawang dayak, diabetes, molecular docking, α-glucoside.

ABSTRACT

Several compounds found within Bawang Dayak, including eleutherine and eleutherol, hold promise as potential therapeutic agentsThis research involved molecular docking and Lipinski rule analysis of 13 ligands derived from flavonoids extracted from bawang dayak. The control ligand, acarbose, was found to form four hydrogen bonds with key amino acids (Gln279, Lys156, Asp242, and Glu411), resulting in a binding energy of -9.8 kcal mol-1. Among the ligands, Ligand 3 displayed a lower binding energy of -9.9 kcal mol-1 compared to acarbose and satisfied all five criteria of Lipinski's rule, despite not forming hydrogen bonds. Instead, Ligand 3 exhibited similar hydrophobic interactions as acarbose with amino acids such as Tyr158, Phe178, Val216, Ser240, Asp242, Glu277, Gln279, His280, Arg315, Asp352, Glu411, and Arg442. Several other ligands exhibited binding energies slightly higher than acarbose, such as Ligands 4, 5, and 8, with binding energies of -8.5 kcal mol-1, -8.6 kcal mol-1, and -8.6 kcal mol-1, respectively. Based on this study, Ligands 3, 4, 5, and 8 are considered potential candidates for anti-diabetic agents. These ligands demonstrated binding energies comparable to acarbose, met at least three of the five Lipinski rule criteria, and exhibited similar amino acid interactions with acarbose, indicating their potential effectiveness in managing diabetes.

ABSTRAK

Beberapa senyawa yang ditemukan dalam bawang dayak, termasuk eleutherine dan eleutherol, berpotensi sebagai agen terapi. Penelitian ini melibatkan molekuler docking dan analisis aturan Lipinski terhadap 13 ligan yang berasal dari flavonoid yang diekstraksi dari Bawang Dayak. Ligan kontrol, acarbose, ditemukan membentuk empat ikatan hidrogen dengan asam amino kunci (Gln279, Lys156, Asp242, dan Glu411), menghasilkan energi pengikatan -9,8 kkal mol^{-1}. Di antara ligan, Ligan 3 menunjukkan energi pengikatan yang lebih rendah yaitu -9,9 kkal mol^{-1} dibandingkan dengan acarbose dan memenuhi kelima kriteria aturan Lipinski, meskipun tidak membentuk ikatan hidrogen. Sebaliknya, Ligan 3 menunjukkan interaksi hidrofobik serupa seperti acarbose dengan asam amino seperti Tyr158, Phe178, Val216, Ser240, Asp242, Glu277, Gln279, His280, Arg315, Asp352, Glu411, dan Arg442. Beberapa ligan lain menunjukkan energi pengikatan sedikit lebih tinggi daripada ligan acarbose, seperti Ligan 4, 5, dan 8, dengan energi pengikat masing-masing sebesar -8,5 kkal mol^{-1}, -8,6 kkal mol^{-1}, dan -8,6 kkal mol^{-1}. Berdasarkan penelitian ini, Ligan 3, 4, 5, dan 8 dianggap berpotensi sebagai agen antidiabetes. Ligan-ligan ini menunjukkan energi pengikatan yang sebanding dengan acarbose, memenuhi setidaknya tiga dari lima kriteria aturan Lipinski, dan menunjukkan interaksi asam amino yang serupa dengan acarbose, yang menunjukkan potensi efektivitasnya dalam mengelola diabetes.

How to Cite

Ariefin, M., & Kalalinggi, S. Y. (2023). Inhibition Mechanism of Component Extract of Bawang Dayak On Diabetes Via Molecular Docking Study. *SPIN-Jurnal Kimia & Pendidikan Kimia*. 5(2). 305-317.

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p-ISSN: 2580-2623
e-ISSN: 2745-6854

INTRODUCTION

Diabetes stands as one of the top ten leading causes of mortality worldwide and significantly contributes to severe health complications (Ismail *et al.*, 2021). Diabetes mellitus (DM) represents a non-communicable disease, ranking seventh among the leading causes of global mortality by 2019, according to the World Health Organization (WHO, 2020). Indonesia is positioned sixth among the top ten nations with the highest prevalence of diabetes, with 10.3 million cases in 2017, and an anticipated surge to 16.7 million cases annually by 2045 (Puspitasari, 2023). Diabetes is categorized into two primary types: type 1 diabetes mellitus and type 2 diabetes mellitus. Type 1 diabetes is a chronic condition in which the pancreas produces insufficient or no insulin. The American Diabetes Association reports that only 5% of individuals with type 1 diabetes receive a diagnosis. On the other hand, type 2 diabetes, also known as DT2, is the most prevalent form among individuals with diabetes (Afifah, 2016). Type 2 diabetes mellitus, one of the most common metabolic disorders, results from the interplay of two main factors: impaired insulin secretion by pancreatic beta cells and the inability of insulin-sensitive tissues to respond adequately to insulin. Given that insulin release and activity are pivotal components of glucose regulation, the molecular mechanisms governing insulin synthesis, release, and detection are subject to meticulous regulation. A breakdown in any of these mechanisms can lead to metabolic imbalances that drive the progression of the disease (Galicia-Garcia *et al.*, 2020). Type 2 diabetes is a complex condition influenced by a combination of genetic factors related to insulin secretion dysfunction, insulin resistance, and environmental factors such as obesity, overeating, dietary habits, physical inactivity, stress, and the natural aging process (Lestari *et al.*, 2021).

Onions, originally native to North America, have a longstanding presence in Asia. In 1912, Merril assigned the name Eleutherine palmifolia L. Merr to the onions found in the Philippines, which is now recognized as synonymous with Sisyrinchium palmifolium L (Febrinda *et al.*, 2021a). Bawang Dayak (*Eleutherine palmifolia* (L.) Merr) is a plant indigenous to Kalimantan, Indonesia, traditionally employed as a medicinal remedy by the Dayak tribe. Local communities have empirically harnessed the healing properties of onions to address various health conditions, including hypertension, elevated cholesterol levels, diabetes, ulcers, constipation, strokes, and as a herbal beverage for post-natal mothers (Prayitno & Mukti, 2018; Galingging, 2009; Harlita *et al.*, 2018a). The Dayak tribe commonly utilizes Bawang Dayak, (*Eleutherine palmifolia* (L.) Merr), by incorporating it into their daily regimen, ingesting it three times a day, with a single consumption of two onions each time. Additionally, it is employed as a treatment for cancer by drying the onions and chewing them directly (Naspiah *et al.*, 2014).). Onion plants have also been employed as a remedy for diarrhea in the form of a tea (M. S. Nascimento *et al.*, 2012).

Phytochemical assessments revealed distinct compounds in different extracts of Bawang Dayak (*Eleutherine palmifolia* (L.) Merr): the n-hexane extract contains secondary steroid metabolites, the ethyl acetate extract contains alkaloids and

steroids, and the ethanol extract is rich in secondary metabolites, predominantly consisting of flavonoids, triterpenoids, and tannins. These extracts of Bawang Dayak exhibited significant antibacterial activity against pathogenic bacteria, most notably MRSA, B. cereus, Shigella sp., and P. aeruginosa, with the highest inhibitory activity observed at a concentration of 10 mg/mL. The minimum inhibitory concentrations for these extracts against MRSAs, B. cereus, Shigella sp., and P. aeruginosa were determined to be 2 mg/mL. Notably, the ethyl acetate extract displayed the most potent antimicrobial effect against B. cereus, with an impressive inhibition rate of 139.58% (Harlita *et al.*, 2018b). Bawang Dayak, *Eleutherine palmifolia* (L.) Merr, is a plant enriched with flavonoid compounds, traditionally utilized by the Dayak tribe in Central Kalimantan for its anti-cancer properties (Pitaloka *et al.*, 2023). Furthermore, research conducted by Mutiah *et al.* (2019) employed a cytotoxic test of HeLa cells using MTT analysis on an ethyl fraction of ethyl acetate from Bawang Dayak E. palmifolia bulbs, revealing an IC50 value of 44.34±9.45µg/mL, categorizing it as a potent anti-cancer candidate. The identification of active compounds within the ethyl acetate fraction revealed 28 chemical compounds, with isoliquiritigenin and oxyresveratrol representing the two compounds with the highest percentage areas (Mutiah *et al.*, 2019).

E. americana acetone extract has yielded three new compounds: eleuthraquinone A, eleuthraquinone B, and eleucanarol, as reported by Mahabusarakam *et al.* in 2010 (Mahabusarakam *et al.*, 2010). Additionally, Chen *et al.* conducted a study on the bulbs of Eleutherine americana, discovering five new naphthalene derivative compounds: Eleutherol A, Eleutherol B, Eleutherol C, Eleuthinone A, and Eleuthinone B in 2018 (Chen *et al.*, 2018). These five compounds exhibit significant effects on human umbilical vein endothelial cells (HUVECs) exposed to high glucose concentrations in vitro. Hongconin, an isolated compound from Eleutherine bulbosa, was identified using LR-EIMS and 1D-2D NMR analysis. The antibacterial activity test of the Hongconine extract and the isolated compounds demonstrated that the extract possesses moderate to moderately strong antibacterial activity against B. subtilis, S. aureus, and K. pneumoniae, with KHM values ranging from 100 to 200 g/ml. On the other hand, the isolated component, Hongconin, exhibited weak antibacterial activity against all tested pathogenic bacteria, with a KHM value exceeding 200 M (Rakainsa & Nisa, 2021). Bawang Dayak has shown potential in addressing diabetes, with in vitro research conducted by Leyama *et al.* (Ieyama *et al.*, 2011) successfully isolating an eleutherinoside compound from the methanol extract of garlic that possesses the capability to inhibit the enzyme alpha-glucosidase (Ieyama *et al.*, 2011). Furthermore, Febrinda *et al.* validated the benefits of garlic water extract in diabetic mice in vivo. The administration of garlic water extract at a dose of 100 mg/kg of body weight for 28 days resulted in lowered blood glucose levels and increased serum insulin levels (Febrinda *et al.*, 2021b).

In silico testing of compounds found in Bawang Dayak (*E. palmifolia* (L.) Merr) revealed that eleuthraquinone A exhibits the lowest G value when compared to other compounds, even in comparison to 5-fluorouracil. This compound also demonstrates a binding energy value of -

9.41 kcal/mol, primarily attributed to hydrogen bonding with the amino acid residues GLU122, LEU124, and LYS61. Importantly, Eleuthraquinone A complies with all Lipinski rules, as detailed by Pitaloka *et al*. in 2023 (Pitaloka *et al*., 2023). Molecular docking studies, a computational approach, are used to identify the ligand that best fits a protein binding site geometrically and possesses the lowest energy (Pinzi & Rastelli, 2019). These methods are valuable for exploring interactions between molecular ligands and protein targets in vitro. In the quest for potential anti-diabetes treatments, this research involved the examination of secondary metabolites from Dayak umbi that had not been previously investigated. These findings were then combined with Lipinski's Rule and ADMET predictions as part of the effort to discover novel therapeutic options for diabetes.

METHODS

Hardware and software

The molecular docking was done using laptop with Intel Core i5-7th generation with speed 2.5 GHz and random-access memory (RAM) 8 Gb with GPU NVIDIA Gforce 930 MX 2Gb. Molecular docking simulation was conducted using Autodock Vina and Autodock Tools 1.5.6 programs (The Scripps Institute, USA). The results of molecular docking were analyzed using Biovia Discovery Studio (downloaded form https://discover.3ds.com). ADMET and toxicity of ligand was analyzed using inline tools through http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp for drug like analyzed (Lipinski rule) and Toxmed to predict toxcity.

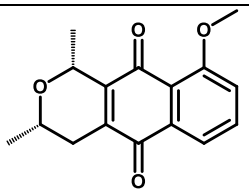
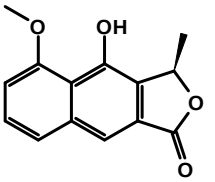
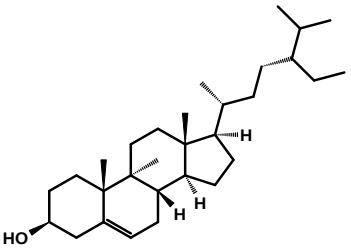
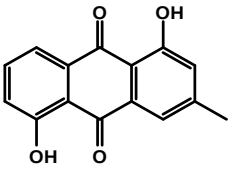
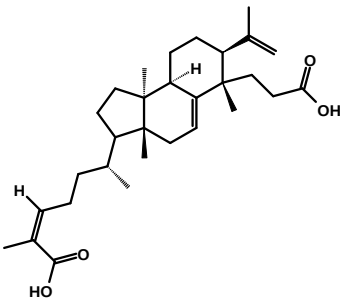
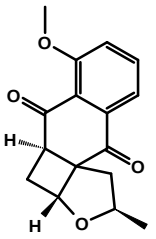
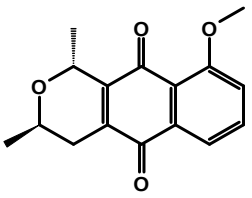
Druglikeness using Lipinski's rule of five

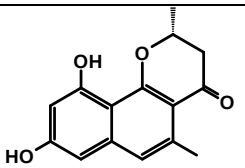
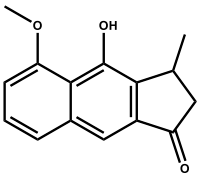
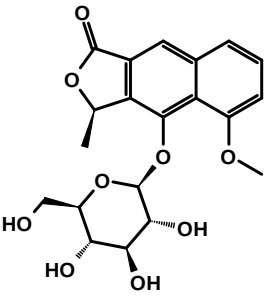
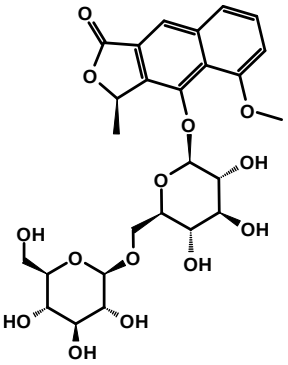
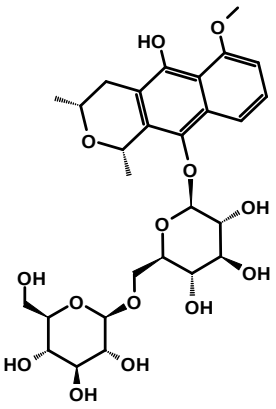
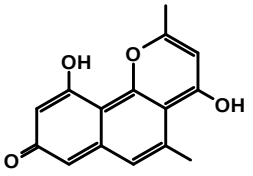
Lipinski rule of five is used to predict the drug likenes of compound or to determne the ability of compound to be drug. Based on Lipinski, the ability of compound to be a drug can be considered based on the five criteria such as, the molecular weight is less than 500 g mol^{-1}, log P value is < 5, the value of hyrogen bonding acceptor (HBA) ≤ 10, hydrogen bonding donor (HBD) should be ≤ 5, and the refractivity of compound in range of 40-130 (Lipinski, 2004; Lipinski *et al*., 2001).

Protein and Ligand Preparation

The crystal structure of protein target was obtainde from protein data bank (PDB) from https://www.rcsb.org/. The crystal structure of α-glucosidase with PDB ID: 3A4A was downloaded in .pdb format. Protein file in .pdb format was opened using Biovia Discvory studio. Water molecules in the crystal stucture were deleted and the native ligand was extracted. The ligand of this study was natural compound isolated from bawang dayak (*E.americana*) (Lubis, 2020). Ligand structures were downloaded from PubChem and save in .sdf format. Ligands with .sdf format were open using Open Babel and convert to .mol2 format. After that, ligand files were opened using Autodock tools 1.5.6 to optimization and save as .pdbqt file. The ligand structure contained in bawang dayak is available in table 1.

Table 1. Natural compound from bawang dayak extract

Compound	Name	Structure
1	Eleutherine	
2	Eleutherol	
3	Beta sitosterol	
4	1,5-dihidroxy-3-methylanthraquinone	
5	Kadsuric acid	
6	Elecanine	
7	Isoeleutherine	

Compound	Name	Structure
8	Dihydroeleutherinol	
9	Isoeleutherol	
10	Eleuthoside A	
11	Eleuthoside B	
12	Eleuthoside C	
13	Eleutherinol	

Molecular docking simulation

Molecular docking was done using specific docking by targeting active site of α-glucosidase protein. the molecular docking was done using Autodock Tool 1.5.6 and autodock vina (Trott & Olson, 2009). The central position of grid was adjusted to x = 25.244, y = -6.076, and z = 29.558 with the grid size $40 \times 40 \times 40$. The exhaustiveness was set in 64 with num modes 10 to increase molecular bonding. The simulation validation was done using redocking method. Native ligand was extracted from crystal structure. Molecular docking methods was valid if the native ligand can occupy the active and the RMSD value < 2.o Å.

RESULTS AND DISCUSSION

Lipinksi rule of five

Drug will distribute throughout body and penetrate the wall cell to reach protein target (receptor). Therefore, drug candidates must have appropriate properties related to pharmaclogy like lipophilicity, the molecular massm or refractivity, to reach protein target. The Lipinski's rule of five predict these molecular properties to know the behaviour of compound as a drug. The Lipinskis prediction of 13 natural compounds from bawang dayak is available in table 2.

Table 2. Results of Lipinskis rule of five tests for ligand compound

Ligand	Molecular Mass	HBD	HBA	LogP	Molar Refractivity
1	272	0	4	2.33	72.374
2	244	1	4	2.79	65.995
3	414	1	1	8.02	128.217
4	254	2	4	2.18	67.816
5	468	0	4	4.99	132.176
6	272	0	4	2.02	70.213
7	272	0	4	2.33	72.373
8	258	2	4	2.91	71.052
9	244	1	4	2.79	65.995
10	406	4	9	-0,43	98.297
11	568	7	14	-1.91	131.359
12	598	8	14	-1.71	140.641
13	256	2	4	3.05	69.847
acarbose	312	5	6	-0.05	77.146

The result show that 11 ligands from bawang dayak m*et al*l criteria of Lipinski's rules of five. Ligands **11** and **12** only met 2 of 5 criteria, because it has molecular mass more than 500 Da, HBA > 5, and HBD > 10. Based on the report of Syahputra et. al., compound with molecular mass more than 500 Da is too big to penetrate the wall cell due to it diffusion ability. In other hand, molecules with molecular mass less than 500 is easier to penetrate the wall cell. Hig HBD or HBA value of compound mean the compound will slower to reach protein target because it can interact strongly with other molecules by hydrogen bonding.

The absence of hydroxyl or amino group in ligand **1**, **5**, **6**, and **7** resulting in value of HBD. Hydrogen atom in hydroxyl or amino group can act as hydrogen donor. Otherwise, the lone pair electron in oxygen atom in carbonyl or hydroxy group can act as hydrigen bond acceptor. Ligand **1**, **5**, **6**, and **7** still has HBA even though it does not have HBD because of the lone pair electrons in oxygen atom, either in hydroxyl or carbonyl group. Ligand **10, 11**, and **12** have more than 10 of HBA because in their structure, these ligands have many lone pair electrons from their hydroxyl or carbonyl group.

LogP value represents the partition coeffficient or distribution of compound between nonpolar and polar solvent. Negative value of logP represent that the

compound has high affinity to water solvent (water phase), otherwise greater value of logP means the compound will more dissolve in nonpolar solvent like lipid. Based on that definition, logP value can be represent the lipophilicity properties of compund. Compound with too high value of logP mean it may be difficult to excrate and leading to accumulation that will impact as a toxic in body. Eleven ligands test has logP value in range of 0-5, excpet compound **3**, **10**, **11**, and **12**. Ligand **3** has value of LogP more than 5.00, this mean it may have potential to be toxic in body due its poor to excrate from body. In other hand, ligands **10**, **11**, and **12** have too small value of logP. It means that these ligands have poor ability to penetrates cells membrane that contain lipid. The small of log P value of **10**, **11**, and **12** due to the highest number of hydrxyl group thereby it can easily to bind with water than lipid. Otherwise, the structure of ligand **3** are hydrocarbon. Hydrocarbon is nonpolar molecules allowing it more dissolve in nonpolar solvent like lipid or octane.

Molecular Docking Results

The validation of molecular docking was done by redocking method. The native ligand was extracted from crystal structure file and docked back to the same binding pocket of protein. Method sai valid if the value of root means square deviation (RMSD) of original position and redocking method is less than 2 Å. In this case, the RMSD result is 1.287 Å, therefore the methods used in this exeriment is valid.

The molecular docking of 13 ligand test from natural compound of extract bawang dayak were conducted using Autodock Vina. The ligand was placed in the same active site or binding pocket of α-glucosidase. The result of molecular docking is binding interaction, binding pose, and binding energy. Binding energy represent the interaction stability of ligand-protein interactions. More negative binding energy mean more stable the interaction. Ligand interaction and binding energy of 13 ligand test is available in table 3.

Table 3. Binding energy and ligand interaction of 13 ligand test

Compound	Binding energy	Interaction	
		Hydrophobic interaction	Hydrogen bonding
1	-7.6	Tyr158, Phe159, Phe178, Val216, Glu277, His280, Phe303, Asp307, Ser311, Pro312, Arg315, Glu411, Arg442	Gln 279
2	-7.4	Lys156, Ser157, Tyr158, Phe159, Ser240, Asp242, Gln279, His280, Phe314 Arg315, Tyr316, Glu411	Gly160, Asn415
3	-9.9	Asp69, Tyr72, His112, Tyr158, Phe159, Phe178, Gln182, Arg213, Asp215, Val216, Ser240, Asp242, Glu277, Gln279, His280, Phe303, Arg315, His351, Asp352, Glu411, Arg442, Arg446,	-
4	-8.5	Asp69, Tyr158, Phe159, Phe178, Val216, Glu277, Phe303, Arg315, Tyr316, Asn415, Arg442	Gln279, Asp352
5	-8.6	Ser157, Tyr158, Phe159, Gly160, Phe178, Val216, Gln279, His280, Ser311, Phe303, Pro312, Leu313, Phe314, Tyr316, Asp352, Gln353, Glu411, Asn415, Arg442	Lys156, Arg315
6	-8.3	Tyr158, Phe159, Phe178, Glu277, Gln279, Phe303, Asp307, Pro312, Arg315Asp352, Arg442	His280, Glu411
7	-7.7	Tyr158, His280, Phe303, Asp307, Thr310, Ser311 Pro312, Leu313, Phe314, Arg315, Gln358, Glu411	-
8	-8.6	Lys156, Ser157, Tyr158, Leu177, Ser240, Asp242, Pro312, Phe314, Asn415	Ser241, Arg315

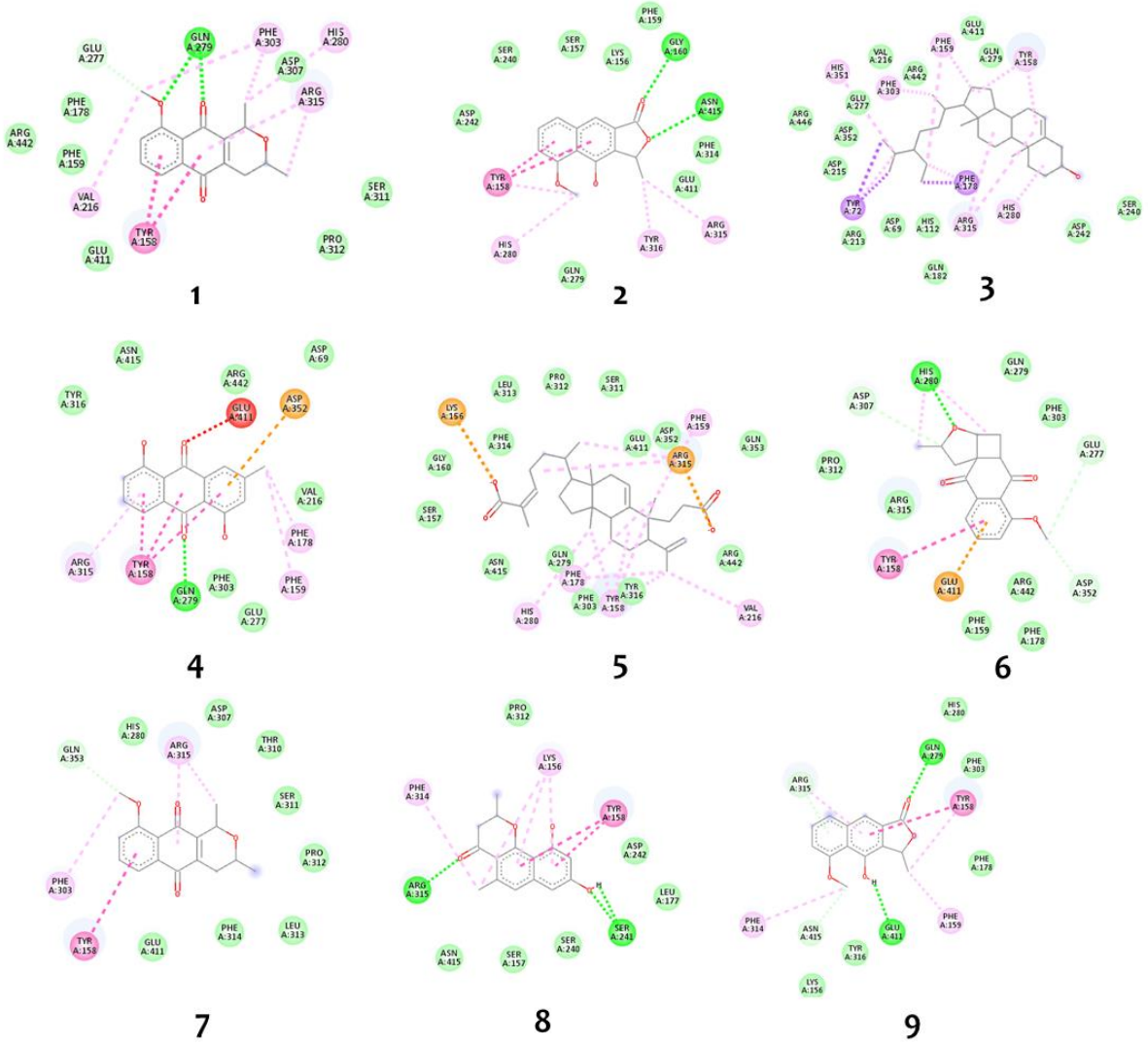
Compound	Binding energy	Interaction	
		Hydrophobic interaction	Hydrogen bonding
9	-7.4	Lys156, Tyr158, Phe159, Phe178, Arg315, His280, Phe303, Phe314, Tyr316, Asn415	Gln279, Glu411
10	-8.9	Asp242, Phe303, Asp307, Gln279, His280, Asn350, Glu277, Arg442, Phe178, Phe159, Phe314, Tyr316, Asn415, Arg315	Tyr158, Glu411
11	-9.8	Ser241, Lys156, Ser157, Asn415m Val216, Glu277, Asp352, Phe159, Phe178, Thr310, Pro312, Leu313, Ser311, Asp242 Ser240	Gly160, Gln279, Arg442, Glu411, Asp307
12	-9.9	Thr237, His423, Asp233, Arg442, Phe159, Tyr158, Phe178, Gln279, Asp352, Asp307, Phe303, His280, Phe314, Leu313, Asn415, Gly160, Ile419, Trp238	Glu422, Ser236, Lys156, Arg315, Gly161
13	-8.2	Lys156, Ser157, Gly160, Asn415, His280, Tyr158, Asp242, Ser240, Tyr316, Phe314, Arg315	Ser241
Acarbose*	-9.2	His280, Phe314, Leu313, Ser240, Asp233, Val232, Arg315, Asp307, Tyr158, Pro312, Ser157, Val216, Phe178, Arg442, Glu277, Asp352, Phe303, Gln353	Gln279, Lys156, Asp242, Glu411

*ligand control

The binding interaction have important implications to binding energy, especially hydrogen bonding. But, in other hand, hydrophobic interaction also influences the binding energy of ligand-protein. In this study, acarbose is used as ligand control because acarbose is an effective α-glucosidase inhibitor. Acarbose can interact with protein and exhibit some hydrogen bonding interactions with Lys156, Asp242, Gln279, and Glu411. α-glucosidase acarbose complex presented -9.2 kcal mol^{-1} binding energy. In other hand, acarbose also can form hydrophobic interaction with some of amino acid residu such as His280, Phe314, Leu313, Ser240, Asp232, etc. The complte interaction of acarbose-α-glucosidase s available in **table** 3. Acarbose is one of effecive inhibitor of enzym α-glucosidase, but it has some side effect such as primarily gastrointestinal nature and other disoreder conditions if patient use it for more than 5 years. Ligand **12** has same binding energy with acarbose, but it only meets two of five criteria in Lipinski rules activity. Moreover, binding energy of ligand **11** also has slightly different with acarbose, but it also fullfill two of five Lipinski criteria.

First most lower binding energy in this study is ligand **3**. Ligand **3** presented -9.9 kcal mol^{-1}, lower binding energy than acarbose. In the catalytic side, ligand **3** only can form hydrophobic interactions with some amino acid residue. However, ligand **3** can perform same interaction with acarbose such as Tyr158, Phe178, Val216, Ser240, Asp242, Glu277, Gln279, His280, Arg315, Asp352, Glu411, Arg442. Ligand **3** also form $\pi - \sigma$ interaction such as with Tyr72 and Phe178. The second lower binding energy is ligand **5**. In catalytic inhibition, ligand **5** displayed twi hydrogen bonding between Lys156 and Ag315 with oxygen atom in carboxylic group and exhibit same hydrophobic interaction with Ser157, Tyr158, Phe178, Val216, His280, Phe303, Pro312, Leu313, Phe314, Asp352, Gln353, Arg442. Ligan **8** exhibit same binding energy with ligand **5.** Inhibition by ligand **8** gave rise 2 hydrogen bonding between OH grup and oxygen of carboyl group with Ser214 and Arg315. Ligand **8** also exhibit same hydrophobic interaction as acarbose with Lys156, Ser157, Tyr158, Ser240, Asp242, Pro312, Phe314. The difference between ligand **8** and acarbose is Asp242 show hydrophobic interactions with

ligand **8**, but it shows hydrogen bonding with acarbose. This difference will influence the binding energy of bith ligand. Hydrogen bonding give more stable binding than hydrophobic interactions. Therefore, the binding energy of ligand **8** is lower than acarbose. The third lower binding energy is ligand **4**. Ligand **4** interact with protein target by -8.5 kcal mol^{-1} and exhibit tw hydrogen bonding with Gln279 and Aps352. In other hand, it also forms hydrophobic interaction with Asp69, Tyr158, Phe159, Phe178, Val216, Glu277, Phe303, Arg315, Tyr316, Asn415, Arg442 in allosteric catalytic site, some of them is same interaction as acarbose. The binding pose and interaction of 13 ligand is available in figure 2.



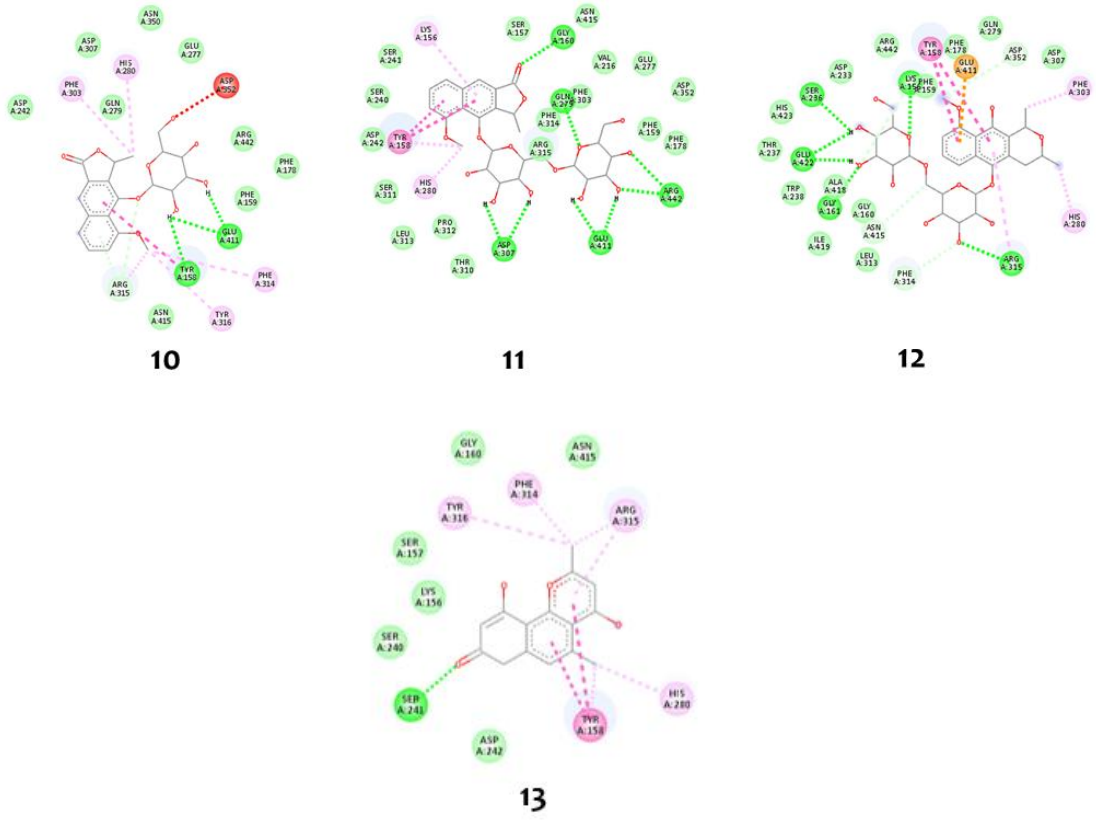


Figure 2. Interaction of ligand and protein of α-glucosidase

CONCLUSION

The molecular docking and Lipinski rules of five of 13 ligands from flavonoid of extracted Bawang dayak (*Eleutherine americana)*. The control ligand of this study, acarbose, form four hydrogen bonding with Gln279, Lys156, Asp242, Glu411 and the binding energy is -9.8 kcal mol^{-1}. The binding energy of ligand **3** is -9.9 kcal mol^{-1}, lower than acarbose and fulfill 5 of five criteria of Lipinskis rule. Eventhough ligand **3** don't have any hydrogen bonding, it forms some similar interactions of hydrophobic as acarbse, like Tyr158, Phe178, Val216, Ser240, Asp242, Glu277, Gln279, His280, Arg315, Asp352, Glu411, Arg442. The other ligand has higher binding energy, but some ligands have slightly higher binding energy than acarbose, like ligand **4, 5,** and **8** with binding energy respectively -8.5 kcal mol^{-1}, -8.6 kcal mol^{-1}, and -8.6 kcal mol^{-1}. Based on the study, ligands 3, 4, 5, and 8 are expected to function as anti-diabetics because they have binding energy similar to acarbose, meet a minimum of three of the five criteria of the Lipinski rules, and have similar amino acid interactions with acarbose.

ACKNOWLEDGEMENT

Gracious appreciation is extended to Chemistry Study Program of Mathematic and Natural Science Faculty, Palangka Raya University for their gracious provision of the facilities required to conduct this research.

REFERENCES

Afifah, H. N. (2016). 10367-20815-1-PB. *Majalah Farmasetika*, *1*(4), 1–4.

Chen, D.-L., Hu, M.-G., Liu, Y.-Y., Li, R.-T., Yu, M., Xu, X.-D., & Ma, G.-X. (2018). New Naphthalene Derivatives from the Bulbs of Eleutherine americana with Their Protective Effect on the Injury of HUVECs. *Molecules*, *23*(9), 2111.

https://doi.org/10.3390/molecules23092111

Febrinda, A. E., Nurwitri, C. C., & Husyairi, K. A. (2021a). Aktivitas Antioksidan Dan Preferensi Konsumen Pada Minuman Fungsional Berbasis Umbi Bawang Dayak. *Jurnal Sains Terapan*, *11*(2), 11–19. https://doi.org/10.29244/jstsv.11.2.11-19

Febrinda, A. E., Nurwitri, C. C., & Husyairi, K. A. (2021b). Aktivitas Antioksidan Dan Preferensi Konsumen Pada Minuman Fungsional Berbasis Umbi Bawang Dayak. *Jurnal Sains Terapan*, *11*(2), 11–19. https://doi.org/10.29244/jstsv.11.2.11-19

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

Galingging, R. Y. (2009). Bawang dayak (Eleutherine palmifolia) as multifunction medicinal plants. *Warta Penelitian Dan Pengembangan*, *15*(3), 2–4.

Harlita, T. D., -, O., & Asnani, A. (2018a). The Antibacterial Activity of Dayak Onion (Eleutherine palmifolia (L.) Merr) towards Pathogenic Bacteria. *Tropical Life Sciences Research*, *29*(2), 39–52. https://doi.org/10.21315/tlsr2018.29.2.4

Harlita, T. D., -, O., & Asnani, A. (2018b). The Antibacterial Activity of Dayak Onion (Eleutherine palmifolia (L.) Merr) towards Pathogenic Bacteria. *Tropical Life Sciences Research*, *29*(2), 39–52. https://doi.org/10.21315/tlsr2018.29.2.4

Ieyama, T., Gunawan-Puteri, M. D. P. T., & Kawabata, J. (2011). α-Glucosidase inhibitors from the bulb of Eleutherine americana. *Food Chemistry*, *128*(2), 308–311. https://doi.org/10.1016/j.foodchem.2011.03.021

Ismail, L., Materwala, H., & Al Kaabi, J. (2021). Association of risk factors with type 2 diabetes: A systematic review. *Computational and Structural Biotechnology Journal*, *19*, 1759–1785. https://doi.org/10.1016/j.csbj.2021.03.003

Lestari., Zulkarnain., & Kaabi, J. A. (2021). Diabetes Melitus: Review Etiologi, Patofisiologi, Gejala, Penyebab, Cara Pemeriksaan, Cara Pengobatan dan Cara Pencegahan. *Prosiding Biologi Achieving the Sustainable Development Goals with Biodiversity in Confronting Climate Change*, 237–241. https://doi.org/10.24252/psb.v7i1.24229

Lipinski, C. A. (2004). Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, *1*(4), 337–341. https://doi.org/10.1016/j.ddtec.2004.11.007

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings 1PII of original article: S0169-409X(96)00423-1. The article was originally published in Advanced Drug Delivery Reviews 23 (1997) 3–25. 1. *Advanced Drug Delivery Reviews*, *46*(1–3), 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0

Lubis, I. A. (2020). Kandungan Fitokimia Serta Kajian Etnofarmakologi Bawang Sabrang (Eleutherine bulbosa (Mill.) Urb). *Jurnal Kedokteran Ibnu Nafis*. 9 (2). 85-92. https://doi.org/10.30743/jkin.v9i2.134

Mahabusarakam, W., Hemtasin, C., Chakthong, S., Voravuthikunchai, S., & Olawumi, I. (2010). Naphthoquinones, Anthraquinones

and Naphthalene Derivatives from the Bulbs of *Eleutherine americana*. *Planta Medica*, *76*(04), 345–349. https://doi.org/10.1055/s-0029-1186143

Mutiah, R., Minggarwati, T. S., Kristanti, R. A., & Susanti, E. (2019). Compound Identification and Anticancer Activity of Ethyl Acetate Fraction from Bawang Sabrang (Eleutherine palmifolia (L.) Merr.) on HeLa Cervical Cancer Cell Line. *Indonesian Journal of Cancer Chemoprevention*, *10*(3), 131. https://doi.org/10.14499/indonesianjcanchemoprev10iss3pp131-139

Nascimento, M. S., Vieira, J. M. S., Malheiros, L. C. S., Silva junior, J. O. C., Rodrigues, L. C. S., & Barbosa, W. L. R. (2012). Characterisation Of Isoeleutherine in Aqueous Extract Of Eleutherine Plicata Herb, Iridaceae, Active Against Entamoeba Hystolitica/ Entamoeba Dispar In-Vitro. *International Journal of Pharmaceutical Sciences and Research*, *3*(4), 1096–1100. http://www.ijpsr.com/V3I4/25%20Vol.%203,%20Issue%204,%20April%202012-1154,%20Paper%2025.pdf

Naspiah, N., Iskandar, Y., & Moektiwardoyo, M. (2014). Artikel Ulasan: Bawang Tiwai (Eleutherine Americana Merr.), Tanaman Multiguna. *Indonesian Journal of Applied Sciences*, *4*(2). 18-30. https://doi.org/10.24198/.v4i2.16820

Pinzi, L., & Rastelli, G. (2019). Molecular Docking: Shifting Paradigms in Drug Discovery. *International Journal of Molecular Sciences*, *20*(18), 4331. https://doi.org/10.3390/ijms20184331

Pitaloka, A. D., Nurhijriah, C. Y., Musyaffa, H. A., & Azzahra, A. M. (2023). Penambatan Molekuler Konstituen Kimia Tumbuhan Bawang Dayak (Eleutherine Palmifolia (L.) Merr) Terhadap Reseptor Vhr Sebagai Kandidat Obat Antikanker Serviks. *Indonesian Journal of Biological Pharmacy*. 3(2). 83-95. https://doi.org/10.24198/ijbp.v3i2.45221

Prayitno, B., & Mukti, b. H. (2018). Optimasi Potensi Bawang Dayak (Eleutherine sp.) sebagai Bahan Obat Alternatif. *Jurnal Pendidikan Hayati*, *4*(3), 149–158. https://doi.org/10.33654/jph.v4i3.436

Puspitasari, L. (2023). *Fakta Penyakit Diabetes di Indonesia dan Cara Mencegahnya*. Https://Www.Siloamhospitals.Com/En/Informasi-Siloam/Artikel/Angka-Diabetes-Di-Indonesia-Semakin-Tinggi-Berikut-Faktanya-1 .

Rakainsa, S. K., & Nisa, K. (2021). Isolasi Dan Elusidasi Struktur Senyawa Dari Ekstrak Bawang Dayak Serta Uji Aktivitas Antibakterinya. *JIFI (Jurnal Ilmiah Farmasi Imelda)*, *4*(2), 43–50. https://doi.org/10.52943/jifarmasi.v4i2.501

Trott, O., & Olson, A. J. (2009). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*. 31(2). 455-461. https://doi.org/10.1002/jcc.21334

WHO. (2020). *The Top 10 Causes of Death*. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/the-Top-10-Causes-of-Death