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Molecular Docking of the Bioactive Compound *Physalis angulata* as an Activator of *Superoxide Dismutase* 1

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ABSTRACT

Physalis angulata was known for its pharmacological potential, including antioxidant activity, yet the specific bioactive compounds responsible for enhancing endogenous antioxidant enzymes, such as superoxide dismutase 1 (SOD 1), remained unclear. This study aimed to identify and evaluate the active compounds of *P. angulata* as natural SOD 1 activators using an *In silico* molecular docking approach. Forty-nine ligands derived from the active constituents of *P. angulata* were screened based on Lipinski's Rule of Five and ADMET properties. Molecular docking was performed using the SOD 1 protein (PDB ID: 5YTO), and docking validation yielded an RMSD value of 0.005 Å. Among the test ligands, withanolide exhibited the most favorable binding energy (−7.011 kcal/mol) and the lowest inhibition constant (7.0 pM), forming strong interactions with key catalytic residues of the enzyme. These findings indicated that withanolide had promising potential as a natural SOD 1 activator, providing a basis for future antioxidant drug discovery.

1. Introduction

Antioxidants are compounds that function to inhibit, delay, or prevent the oxidation process of easily oxidized substances. These compounds act as inhibitors by reacting with reactive free radicals and then converting them into a more stable and harmless form (Reubun, 2022). According to the source, antioxidants can be classified as either endogenous (produced within the body) or exogenous (sourced from outside the body). Endogenous antioxidants are essential in reducing the oxidative harm induced by free radicals, with key enzymes involved including catalase, glutathione peroxidase, and superoxide dismutase (SOD) (Murray *et al*., 2014). SODs are enzymes containing metal that protect the body from harmful oxygen-containing molecules. Human cells contain three types of superoxide dismutase (SOD) extracellular SOD (ECSOD), enzymes: manganese SOD (MnSOD), and copper-zinc SOD (CuZnSOD), also known as SOD1. Among these, SOD1 provides cellular protection against oxidative stress resulting from reactive oxygen species (ROS) (Bawono, 2024).

Physalis angulata Linn. commonly known for its use in traditional medicine, contains various bioactive compounds such as flavonoids, alkaloids, tannins, glycosides, and phenolics. The *Physalis angulata* plant contains various steroidal lactones, including physalins A–I and physagulins A–G, as well as withanolides such as withangulatin A and withanolide T. Additionally, the plant yields the flavonol glycoside myricetin 3-O-neohesperidoside (Pillai, 2022). According to Fadhli (2023), P. angulata has demonstrated diverse biological and pharmacological properties. These include activity as an antioxidant, anticancer agent, anti-diabetic, anti-inflammatory, antibacterial, antifibrotic, anti-diarrheal, and antihypercholesterolemic. *In vivo* and *in vitro* studies on rats according to Lestiariani explain that *Physalis angulata* leaf extract for 28 days did not significantly alter kidney or liver function in rats.

The antioxidant properties of *Physalis angulata* have been previously studied; however, the specific bioactive compounds responsible for this activity remain unidentified. Consequently, it is important to determine which active constituents of *Physalis angulata* contribute to the activation of the superoxide dismutase (SOD) enzyme through *In silico* analysis. *In silico* studies, computer-based simulations and analyses are conducted using specialized software. This approach is increasingly developed as an alternative method aimed at limiting, reducing, or even replacing animal testing while still providing valuable insights into the safety and efficacy of pharmaceutical compounds (Siagian, 2022). Therefore, this study aimed to identify the active compounds of *P. angulata* as potential natural activators of SOD1 through *In silico* molecular docking analysis.

2. Methods

2.1. Ligand Preparation

This research used YASARA Structure, PubChem, Discovery Studio Visualizer, PyMol, SMILES, RSCB, and SwissAdme. Forty-nine ligands of *Physalis angulata* compounds were obtained from the PubChem database. Screening was performed based on Lipinski's Rule of Five, which considered parameters such as molecular weight, hydrogen bond donors, hydrogen bond acceptors, lipophilicity (logP), and topological polar surface area (TPSA). Toxicity predictions were conducted using the SwissAdme server to exclude ligands with poor pharmacokinetic or toxicity profiles. Only ligands that passed both screenings were used for molecular docking analysis, and their structures were saved in PDB format.

2.2. Receptor Preparation

The crystal structure of the SOD1 enzyme (PDB ID: 5YTO) was retrieved from the RCSB Protein Data Bank which had the natural ligand naphthalene-catechol. Receptor

preparation was carried out using YASARA Structure by removing water molecules, ions, and co-crystallized ligands to obtain the apoenzyme form of SOD1. Polar hydrogen atoms were added, and missing residues were corrected to ensure structural completeness. The receptor file was then energy-minimized and saved in PDB format for further docking analysis.

2.3. Docking Validation

Validation of the docking protocol was performed using the natural ligand naphthalene-catechol. The docking was conducted within a grid box that surrounded the catalytic site of the Cu/Zn-SOD protein. Several grid box sizes were tested to determine the most optimal configuration, and the selected grid box size was 3.50 Å, which provided the most negative binding energy value. The accuracy of docking was assessed by comparing the re-docked pose of the natural ligand with its crystallographic pose, and the RMSD (Root Mean Square Deviation) value was calculated. An RMSD below 2 Å was considered valid, and in this study, the docking protocol produced an RMSD value of 0.005 Å, indicating excellent reliability of the method.

2.4. Virtual Screening and Docking

This study utilized 49 compound ligands derived from the active constituents of *Physalis angulata* as test ligands. The structure and stability of the selected receptor were initially evaluated. A physicochemical analysis was performed on 25 ligands, which resulted in the elimination of 24 compounds. Virtual screening of the remaining ligands identified those with the most favorable Gibbs free energy values, and five ligands advanced to the final testing stage. Molecular docking was then conducted using YASARA Structure, where each ligand was docked into the active site of the SOD1 receptor. Binding affinity was assessed based on Gibbs free energy (ΔG), and inhibition constants (Ki) were calculated. Ligands with lower binding energies and smaller Ki values were considered to have stronger interactions with the receptor.

2.5. Interaction Analysis

The docking results were analyzed to identify the types of interactions formed between ligands and the receptor. Two-dimensional (2D) interaction maps were generated using Discovery Studio Visualizer, which provided details on hydrogen bonds, hydrophobic contacts, and bond distances. Three-dimensional (3D) visualization was conducted using PyMol to illustrate the spatial arrangement of ligand-receptor complexes.

3. Results and Discussion

3.1. Results

Receptor stability was assessed using PROCHECK, a software tool that generates a Ramachandran plot diagram and associated statistical data. Ramachandran plot diagram displays the distribution of residues in four distinct quadrants, each with a different color: the most favored region, additionally allowed region, generously allowed region, and disallowed region. As shown in Figure 1 the Cu/Zn-SOD 1 (5YTO) receptor analysis shows that amino acid residues occupy out of a total of 1512 residues in the structure, 1197 residues are non-glycine and non-proline used as the basis for assessment. A total of 1077 (89.7%) residues (89.7%) are located within the most favored regions, while 120 residues (10.3%) are found in the additionally allowed regions. Notably, no residues are present in either the generously allowed or disallowed regions, both accounting for 0.0%.

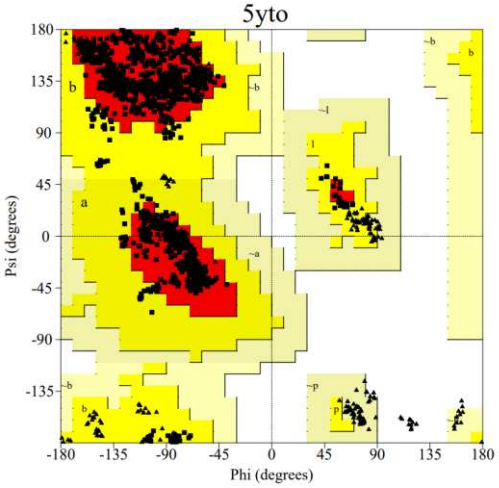

Figure 1 Ramachandran Plot of Cu/Zn Superoxide Dismutase

Table 1 presents the evaluation of Lipinski's Rule of Five, which functions as a reference for evaluating the physicochemical characteristics of both test and reference ligands in the context of drug development, particularly regarding solubility and permeability. According to these criteria, a ligand must comply with at least three rules to be viable for further development. The analysis revealed that seven of the test ligands failed to meet the minimum threshold, thereby disqualifying them from advancing to the next stage and eliminating them as potential drug candidates.

Table 1 Ligand's evaluation of Lipinski's Rule of Five

Ligands	Molecular Mass (Da)	Hydrogen Bond Donors	Hydrogen Bond Acceptors	TPSA (Å²)	GI Absorption	Lipinski; Violation	PAINS #Alerts
Withanolide	470	2	6	96	High	0	0
Luteolin	286	4	6	111.13	High	0	1
Quercetin	302	5	7	131.36	High	0	1
Gallocathecin	306	6	7	130.61	High	1	1
Gallic acid	170	4	5	97.99	High	0	1

Note: yellow box: violates five Lipinski rules

Gridbox validation is conducted to ascertain the precise targeting of the designated active site within the chosen receptor throughout the molecular docking procedure. The best-selected grid box size is 3.50 Å because it has the most negative binding free energy (ΔG) compared to other sizes, which is -7.131 kcal/mol. The binding free energy is obtained from the results of the re-docking napthalene-catechol with its receptor protein. In the molecular docking validation stage, the selected grid box size has the most negative binding free energy value because a lower ΔG value indicates stronger attractive forces between atoms, while repulsive forces are smaller. Therefore, the bond between the receptor's active site and the ligand has a stable conformation (Hasan *et al*., 2022).

The selected grid box has an RMSD value of 0.005 Å. RMSD is used to assess the similarity of poses between natural ligands obtained from crystallography and natural ligands that have been re-docked. An RMSD value is considered good if it is less than 2 Å (Susanti *et al*., 2018; Nursamsiar *et al*., 2020). An RMSD value of less than 2 Å indicates that the re-docked natural ligand has the same pose as its natural counterpart.

Natural ligand napthalene-catechol has a binding free energy value of -7.023 kcal/mol, interacting with 9 amino acid residues shown in Figure 2(a). Hydrogen bonds occur at 6 residues: Gln22, Lys23, Pro28, Val29, Ser98 and Glu100. Pi-stacked interactions occur at

residue Trp32. Pi-alkyl interactions occur at residue Lys30. Salt bridge interactions occur at residue Glu21. Additionally, the other five residues are bonded through Van der Waals interactions. The tested ligand interacts with nine amino acid residues on the target protein, as shown in Figure 2(b). Conventional hydrogen bonds are formed with two residues: Lys23 and Glu21. One carbon-hydrogen bond is identified at the residue Thr2. Alkyl interactions are found at residues Lys23 and Lys30. Meanwhile, Van der Waals interactions occur with Glu100, Pro28, Gln22, and Val29 residues.

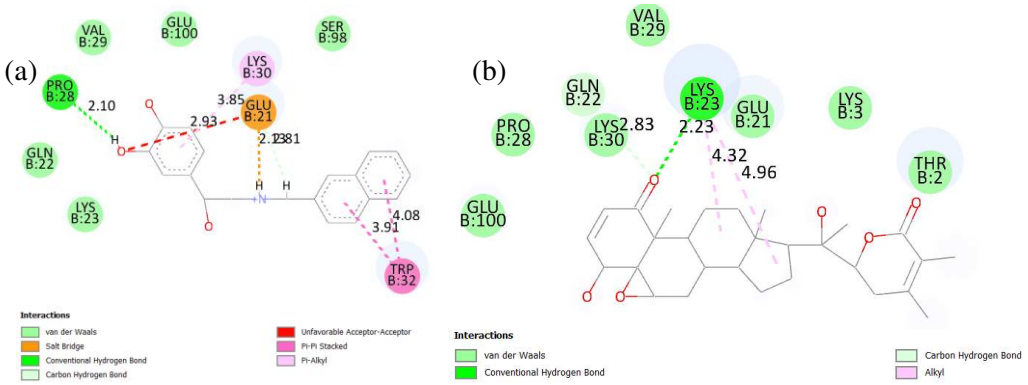

Figure 2 Hydrogen bond and hydrophobic bond. (a) Naphtalene-cathecol; (b) Withanolide

The results of the virtual screening show a variation in the performance of each ligand against the target protein based on three primary parameters: binding energy efficiency, binding energy, and dissociation constant. In the molecular docking of the test compound from the *Physalis angulata* with the SOD enzyme (Table 2), the withanolide exhibits the most favorable performance, characterized by an efficiency value of 0.2062 kcal/(mol·atom), a binding energy of −7.011 kcal/mol, and a dissociation constant of 7,258,867.5 pM. These parameters indicate that withanolide demonstrates the most stable interaction and highest binding affinity toward the target protein when compared to other ligands, including luteolin, quercetin, gallocatechin, and gallic acid.

Table 2 The molecular docking parameters of the test compound with SOD enzyme with *Physalis angulata*

Ligands	Gibbs free energy [kcal/mol]	Inhibition Constant [pM]
Naphtalene-cathecol	-7.023	6.99
Withanolide	-7.011	7.0
Luteolin	-6.400	21.3
Quercetin	-6.195	29.1
Gallocathecin	-5.667	54.6
Gallic acid	-4.662	174.0

Note: yellow box: Natural ligand

3.2. Discussion

Based on the Ramachandran plot, the stability of the receptor structure can be determined by the percentage of residues that fall into the most active area and how few residues fall into the forbidden area (Ruslin *et al*., 2019). According to Suhadi (2019), a receptor is stable if more than 80% of its residues are in the most active area and less than 15% are in the forbidden area. In the analysis results of this study, the receptor showed that 89.7% of residues are in the most active area, and only 10.3% are in the forbidden area. This indicates that the receptor structure has excellent stability, which is also supported by Rao's (2020)

opinion that protein structures can be categorized as having high quality if more than 85% of their residues are in the most active area.

Receptors are prepared by removing water molecules, ions, and ligands to convert the enzyme into an apoenzyme for molecular docking (Maulidia, 2021). The stability analysis of the receptor is conducted using the PROCHECK site through the Ramachandran plot diagram, which visualizes the torsion angles φ (phi) and ψ (psi) as indicators of amino acid residue distribution and the intrinsic quality of the receptor structure (Sobolev *et al*., 2020).

The evaluation of the bioavailability parameters of all test ligands and control ligands (napthalene-catechol) indicates that, in general, these compounds meet the Lipinski rules. The Lipinski rules are guidelines for evaluating the suitability of a compound as an oral drug based on pharmacokinetic parameters, particularly permeability and solubility in the gastrointestinal tract (Lipinski *et al*., 2012). All compounds in the tables have a relative molecular mass below 500 Dalton, which is the threshold in the Lipinski rules. This value indicates that the molecules are small enough to pass through cell membranes via passive diffusion (Lipinski *et al*., 2016). The majority of compounds have an appropriate number of hydrogen bond donors (Hdon) and acceptors (Hacc) according to the criteria (Hdon ≤ 5 and Hacc ≤ 10). However, quercetin and gallocatechin have high Hdon and Hacc values (5 and 7, respectively), although still within the tolerance limits. The increased number of donors and acceptors can affect the increase in molecular polarity, thus reducing membrane permeability (Zhao *et al*., 2021). In addition, the number of hydrogen donors and acceptors in ligands determines the flexibility and adaptability of the ligand to bind with the target enzyme or protein (Jamuna *et al*., 2018).

The Topological Polar Surface Area (TPSA) analysis results show that all tested ligands have values ranging from 96 to 131 Å². TPSA is a physicochemical parameter that evaluates a molecule's polarity and a compound's ability to permeate biological membranes. TPSA represents the sum of all polar atoms, primarily oxygen and nitrogen, including hydrogen bonds (Mugumbate & Overington, 2015; Kumar *et al*., 2017). The recommended TPSA limit for optimal oral absorption is ≤140 Å², while the ideal value for the ability to penetrate the blood-brain barrier is ≤79 Å² (Lipinski, 2012). Violations of Lipinski's rule were not found in most compounds, except for gallocatechin, which violates one criterion, namely the high number of donors/acceptors. For PAINS (Pan-Assay Interference Compounds), several compounds have one alert, such as luteolin, quercetin, gallocatechin, gallic acid, and catechin. Nevertheless, one PAINS alert can still be tolerated in the early development of drug candidates (Baell & Walters, 2014).

The molecular docking method was validated by observing the Root Mean Square Deviation (RMSD) data. The results of the molecular docking method validation involving the receptor 5YTO and its natural ligand obtained an average RMSD value of 0.005 Å and an affinity energy of -7.0 kcal/mol. These results also indicate that the molecular docking method is valid. A smaller RMSD value represents that the position of atoms in the ligand is improving as it approaches the original conformation (Lestari, 2015).

The molecular docking process was carried out on the active region (catalytic site) of the enzyme superoxide dismutase (SOD) using the protein structure with PDB ID 5YTO. According to Bawono (2024), the catalytic site of this enzyme consists of the amino acid residues Lys30, Lys23, Pro28, and Glu100, which serve as the primary reference in evaluating the quality of the interaction between the test ligand and the target receptor. The results of the molecular docking show that the natural ligand (napthalene-catechol) forms hydrogen bonds with the residue Pro28 at a distance of 2.10 Å, and interacts hydrophobically with the four key residues, namely Lys23, Lys30, Pro28, and Glu100, all of which are part of the catalytic site. This indicates an excellent affinity and binding orientation to the enzyme target. Tryptophan 32 (Trp32) and Glutamate 21 (Glu21) are essential amino acids in the stabilization and activation of SOD1. These interactions may support the maturation and activation of SOD under copper and zinc deficiency conditions, as well as in the formation of intra-subunit

disulfide bonds. All test ligands also formed hydrogen bonds similar to the natural ligand naphthalene-catechol at Lys23 and Glu100. Lysine, as a charged residue, and glutamate, as a polar residue, play critical roles in generating a positive electrostatic field within the channel leading to the mature SOD1 active site, thereby enhancing enzymatic function by directing anions electrostatically. The solvent-accessible active site catalyzes the reaction of O_2^- with Cu^{2+} ions (Bawono, 2024).

Based on the results of molecular docking of the active compounds from *Physalis angulata* displayed in Table 2, it is known that the compound with the highest affinity for the SOD enzyme is withanolide, with a binding energy value of -7.011 kcal/mol. It is followed by luteolin, quercetin, gallocatechin, and gallic acid. The test ligand withanolide shows the formation of hydrophobic bonds with Thr2, Lys3, Glu21, Gln22, Lys23, Pro28, Val29, Lys30, and Glu100, as well as hydrogen interactions with the identical key residues, namely Lys23, Lys30, Pro28, and Glu100.

The inhibition constant (Ki) value of 18.2 pM indicates that withanolide only requires a low concentration to inhibit enzyme activity effectively, and this interaction reinforces the hypothesis that withanolide can stably bind within the active site of the SOD enzyme (Klebe, 2013). The increasingly negative affinity energy and the decreasing inhibition constant (Ki) are key indicators in determining the potential of a compound as an enzyme inhibitor (Klebe, 2013). According to Noviardi and Fachrurrazie's (2015) research, there is a direct proportionality between affinity values and Kd values. Their findings further indicate that a more stable complex is characterized by a more negative affinity energy and a lower Kd value.

The visualization results also support this finding, showing that withanolides have interaction patterns consistent with the residues of the catalytic site. The 2D visualization (Figure 2) analysis of the results demonstrates that the ligand and receptor primarily engage through two modes of interaction: hydrogen bonds and hydrophobic interactions. Hydrogen bonds play an important role in nature, such as in protein folding, ligand-protein interactions, and catalytic reactions (Chen *et al*., 2016). According to Rachmania (2019), hydrogen bonds can stabilize the interaction between ligands and receptors and can affect the ΔG value or affinity energy. Hydrophobic interactions also play an important role in ligand-receptor interactions. Hydrophobic interactions can stabilize ligand binding at the target site and help modify the binding affinity and effectiveness of the drug. The increase in the number of hydrophobic atoms on the surface of the active side can further enhance the drug's biological activity (Varma *et al*., 2010).

Hydrogen bonds (H-bonds) are commonly observed interactions between proteins and ligands. In biological systems, such as proteins or receptors, proton donors (hydrogen bond donors) typically involve NH_3 or OH functional groups. These bonds possess substantial strength due to the hydrogen atom being covalently bonded to a highly electronegative atom, resulting in a partial shift of the hydrogen's electron density toward the adjacent atom, thereby stabilizing the interaction (Maulana, 2023). Considering all these parameters, withanolide from *Physalis* is the most promising test compound as a natural inhibitor of the SOD enzyme. It has a high affinity, forming interactions with key residues, and shows low inhibition constants, making it relevant for further development as a natural compound-based antioxidant agent.

4. Conclusion

The active compound of *Physalis angulata* with the greatest potential as a natural activator of the SOD1 enzyme was withanolide. Molecular docking analysis showed that withanolide had the most favorable binding affinity (−7.011 kcal/mol) and the lowest inhibition constant (7.0 pM), with stable interactions at the catalytic site of Cu/Zn-SOD. These

results indicated that withanolide could be developed as a promising candidate for antioxidant drug discovery.

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