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# In-Silico Investigation of Compounds from Black Mangrove (*Rhizophora mucronata* L.) as Inhibitors of Exo-1,3-β-Glucanase in *Candida albicans*

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**Abstract:** *Candida albicans* is an opportunistic fungal pathogen responsible for systemic infections that result in considerable morbidity and mortality. The enzyme Exo-1,3 β-glucanase is essential for cell wall metabolism and pathogenicity in *C. albicans,* rendering it a potential therapeutic target. The study aims to evaluate the effectiveness of bioactive compounds from black mangroves (*Rhizophora mucronata* L.) as inhibitors of Exo-1,3 β-glucanase using an in silico approach. The test results from 28 black mangrove plant compounds yielded a the free energy value (ΔG) with a the inhibition constant (KI) comparable to that of ibrexafungerp. The four compounds exhibited the following properties: β-amyrin (ΔG) = -8.24 kcal/mol with KI = 908.46 nM, lupeol = -8.19 kcal/mol with KI = 994.44 nM, ethyl-iso allocholate = -7.66 kcal/mol with KI = 2.44 μM, and magnolol = -7.2 kcal/mol with KI = 5.25 μM. The molecular docking test results were evaluated from multiple perspectives, specifically the ΔG value generated post-docking, the KI, and the interactions of amino acid bonds and residues with the receptor. The ADMET prediction test results indicate that the four molecular docking test chemicals exhibit commendable skin penetrating capabilities. Based on the results of the tests, the four compounds, namely Ethyl-isoallocholate, β-amyrin, Magnolol, and Lupeol with β-amyrin, have the potential to become new drug candidates as Exo 1-3-(-glucanase inhibitors) in *Candida albicans*

**Keywords:** β-amyrin, *candida albicans*, in silico, lupeol, *Rhizophora mucronata* L.

## 1. INTRODUCTION

*Candida albicans* is the fungus of the genus Candida that causes the most infections. Candida is a normal flora found in the human body, usually found in the respiratory tract, mucosal membranes, reproductive organs, skin and under the fingernails of the feet and hands. In these locations, candida can infect due to a decrease in the immune system of the human body which causes the fungus to be pathogenic and sometimes candida can cause progressive and systemic diseases. *C. albicans* produces 1,3 β-Glucanase which is a hydrolytic enzyme that plays a role in the degradation process of 1,3 β-glucan which is the main component of the fungal cell wall. 1,3 β-Glucanase breaks down polysaccharides on the fungal cell wall into oligosaccharides which then process into a temporary form of hyphae [1], [2].

*Rhizophora mucronata* L. commonly known as black mangrove, is a component of Indonesia's coastal biodiversity. Certain components of mangrove plants, including the stem, leaves, and fruits, are utilized by researchers due to their secondary metabolite chemicals, such as flavonoids, tannins, and sesquiterpenes. *Rhizophora mucronata* L. can serve as antioxidants, antibacterials, and anti-inflammatories [3], [4], [5]. In vitro testing of antifungal activity showed that *Rhizophora mucronata* L. has activity against *Candida albicans* [6]. Based on several studies that have been conducted, there are 28 compounds identified in black mangroves, namely Quinizarin [7]. n-Hexadecanoic acid, phytol, oleic acid [8]. Ethyl iso-allocholate, dasycarpidan-1-methanol acetate, 3-O-methyl-D-glucose,

metacetamol [9]. Syringic acid, catechol, ⍟-amyrin, coumaric acid, octanal, myrcene, hygrine, coumarin, coumaryl alcohol, caffeoyl alcohol, synephrine, scopoletin, glucuronic acid, magnolol, linolenic acid, methyl ellagic acid, lupeol, xanthotoxin, catechin, 3',4',5,7-Tetrahydroxy-3,6,8-trimethoxyflavone [10]. The results are summarized in Table 1.

**Table 1.** The content of black mangrove compounds based on the literature

| No. | Compound name | Group | Refences |
|---|---|---|---|
| 1 | Quinizarin | Quinone | [11] |
| 2 | z n-Hexadecanoic acid | Fatty Acid | [12] |
| 3 | Phytol | Terpenoid | |
| 4 | Oleic acid | Fatty Acid | |
| 5 | Ethyl-iso allocholate | Triterpenoid | [9] |
| 6 | Dasycarpidan-1-methanol acetate | Alkaloid | |
| 7 | 3-O-methyl-D-glucose | Glucose | |
| 8 | Metacetamol | Phenolic | [13] |
| 9 | Syringic acid | Phenolic | |
| 10 | Catechol | Phenolic | |
| 11 | Beta-amyrin | Triterpenoid | |
| 12 | Coumaric acid | Phenolic | |
| 13 | Octanal | Aldehyde | |
| 14 | Myrcene | Terpenoid | |
| 15 | Hygrine | Alkaloid | |
| 16 | Coumarin | Heterocycle Phenolic | |
| 17 | Coumaryl alcohol | Phenolic | |
| 18 | Caffeoyl alcohol | Phenolic | |
| 19 | Synephrine | Alkaloid | |
| 20 | Scopoletin | Heterocycle Phenolic | |
| 21 | Glucuronic acid | Carbohydrate | |
| 22 | Magnolol | Polyphenol | |
| 23 | Linolenic acid | Fatty Acid | |
| 24 | Methyl ellagic acid | Polyphenol | |
| 25 | Lupeol | Triterpenoid | |
| 26 | Xanthotoxin | Heterocycle Phenolic | |
| 27 | Cathecin | Flavonoid | |
| 28 | 3' ,4' , 5, 7- Tetrahydrxy-3,6,8 trimethoxyflavon | Flavonoid | |

Based on data from Table 1, tests were carried out on compounds that have been reported to be contained in black mangroves that have the potential to be inhibitors of 1,3 β-glucanase in *Candida albicans* in in-silico by looking at their bond affinity and predicting ADMET values. The objective of assessing binding affinity and ADMET values through molecular docking is to ascertain the strength of interaction between compounds derived from black mangroves and biological targets, estimate the absorption efficacy of these compounds, evaluate their capacity to reach target tissues, and identify potential toxicity.

## 2. MATERIALS AND METHODS

### *2.1. Materials*

The laptop set uses a 64-bit windows 11 home single language system with operating specifications: Intel Core i5-1235U 1.3 GHz processor, 12 CPUs, 8 GB RAM. The programs used include ChemDraw Ultra 12+Serial, Discovery Studio Visualizer, Autodock Tools 1.5.7, YASARA, SCFBio, pkCSM. A three-dimensional (3D) structure of the receptor protein that can be downloaded from the Protein Data Bank website (https://www.rscb.org/). The model data used is the structure of the protein Exo – 1,3-β-glucanase with receptor code 4M81. The two-dimensional (2D) and three-dimensional (3D) structures of several comparator compounds used as Exo-1,3 beta glucanase

inhibitors ibrexafungerp. Two-dimensional (2D) and three-dimensional (3D) structures of 28 secondary metabolite compounds of black mangrove plants (*Rhizopora mucronata* L.).

*2.2. Methods*

2.2.1. Exo 1,3-β-glucanase Receptor Preparation

The Exo-1,3-β-glucanase receptor data was downloaded in PDB format from https://www.rscb.org with PDB ID code 4M81. Receptor preparation was performed to separate the macromolecule or protein from the native ligand, water molecules, and other unnecessary molecules from the PDB data. The separation was performed using the Discovery Studio application. The receptor, separated from the ligand, was then saved as Receptor.pdb.

2.2.2. Preparation of Comparative Compounds and Test Compounds

The comparative compound used in this study, ibrexafungerp, was searched for in structure on the pubchem website (https://pubchem.ncbi.nlm.nih.gov/) then saved in SDF format in 2D form. Based on the results of the literature total of 28 (Table 1) secondary metabolite compounds contained in black mangrove plants (*Rhizopora mucronata* L.) were obtained in this study. Search for the structure of the test compound is carried out in the same way as in the comparative compound.

2.2.3. Molecular Docking Validation

The molecular docking *validation process* is carried out by redocking, between *the native ligand*and the exo 1,3-β glucanase receptor that has been made before. This validation was carried out three times with the Autodock Tools and Autodock4 applications. The method is said to be valid if it has a Root Mean Square Deviation (RMSD) value of < 2 Å. In the validation, the grid box (x=63.3; y=68.6; z=7.5) is set using AutoDock Tools, where the grid box is the space for the ligand to interact with the amino acid residue of the target protein [14].

2.2.4. Molecular Docking

The molecular docking process is carried out on the test ligand and the comparison ligand for each target protein through the AutoDock software using a valid tethering procedure. The results of the *docking* were separated between the receptors with *the native ligands* prepared with the native ligands that were *docked* using the Discovery Studio application. Followed by inserting by means of overlapping native ligands that have been separated into the YASARA application to calculate RMSD or *root mean square deviation*, which is often known as standard deviation, is one of *the docking* parameters. Visualization of molecular docking results was carried out using the Discovery Studio application.

2.2.5. Prediction of Physicochemical Parameters

The prediction of physicochemical parameters in terms of solubility and permeability is determined based on Lipinski"s Rule of Five. Lipinski's Rule of Five testing of the compound's structure was conducted on the SCFbio website (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). The test results obtained molecular weight, P Log value, donor hydrogen bond and acceptor hydrogen bond [15], [16].

2.2.6. ADMET Prediction

In the prediction, ADMET was carried out on 28 compounds from black mangrove (*Rhizopora mucronata* L.). ADMET prediction testing was used to look at the predictions of the absorption, distribution, metabolism, excretion and toxicity of potential compounds that are potential inhibitors of Exo-1,3 beta glukanase and predict their potential to be close to comparators. ADMET prediction testing using the pkCSM website (https://biosig.lab.iq.edu.au/pkcsm) [17].

## 3. RESULTS AND DISCUSSION

*3.1. Method Validation*

The purpose of this method validation is to ensure that the method used in native ligand docking can be trusted as a reference in docking. The parameter used is in the form of Root Mean Square Deviation (RMSD), where the method is said to be valid if RMSD < 2 Å. RMSD is a parameter used to evaluate the docking process that is executed appropriately or not, and describes how much the natural ligand conformation changes before and after validation is carried out [18].

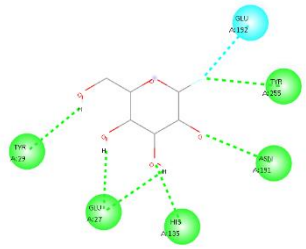
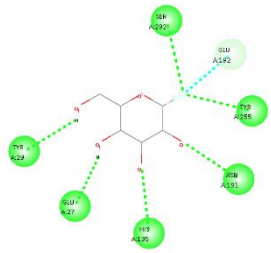
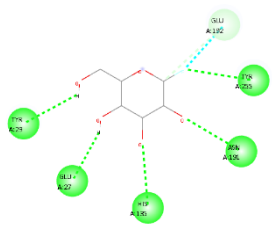
Based on the validation process, a valid docking method was obtained, namely a procedure with grid box parameters x=63.3; y=68.6; z=7.5 and on a space line of 0.900 Å with dimensions of 40x40x40. The docking procedure that has been carried out is declared valid because from 3 replications of native ligand docking, RMSD is less than 2 Å. The mean RMSD value of the Exo 1.3 β-glucanase receptor is 0.5561 Å So that the molecular docking process can be carried out on each compound with the same settings in the validation.

*3.2. Molecular Docking Results Analysis*

Novel antifungal agents are critically required because existing antifungal medications have significant adverse effects, are in short supply, and the emergence of drug-resistant strains is a major concern. The fungal cell wall mostly consists of chitin, glucans, mannans, and glycoproteins essential for adhesion. It serves as a protective barrier. Targeting cell wall constituents and their associated enzymes is a promising avenue for the development of new antifungal medicines. Research on exo-1,3-β-glucanase via molecular docking revealed that the chemicals sesamin, pinoresinol, caflanone, and herbacetin have favorable interactions with binding energy values of -12.21, -11.50, -11.48, and -11.03 kcal/mol, respectively [19].

The results of molecular docking include free energy values, constant inhibitions, and ligand interactions with amino acid residues on receptor proteins. The results of the receptor validation can be seen in Table 2. Comparison of results was carried out by comparing the compound with the comparator drug as a control. In this study, the comparative drug Ibrexafungerp was used. Ibrexafungerp became the first antifungal agent of the triterpenoid group. As a non-azole antifungal, ibrexafungerp can provide broad-spectrum activity performance against several isolates of the candida genus. Ibrexafungerp attacks the 1,3 β-glucan protein which is only present on the fungal cell wall and is not part of the human cell so it will not interact with the cytochrome P450 cells in human cells thus minimizing the side effects that may occur [20], [21], [22].

**Table 2.** Molecular Docking Receptor Validation Results

| No | Visualization | Hydrogen Bond | Secondary Interaction | RMSD |
|---|---|---|---|---|
| 1 |  | GLU27, TYR29, HIS135, ASN191, TYR255 | GLU192 | 0.7135 Å |
| 2 |  | GLU27, TYR29, HIS135, ASN191, TYR255, SER292 | GLU192 | 0.4774 Å |
| 3 |  | GLU27, TYR29, HIS135, ASN191, TYR255 | GLU192 | 0.4775 Å |

The results of testing 28 secondary metabolite compounds of black mangrove plants were obtained with 4 compounds that had a free energy value (ΔG) close to ibrexafungerp (Table 3). The results of the molecular docking test were reviewed and analyzed from several aspects, namely the value of free energy (ΔG) formed after the docking process, the value of the inhibition constant (KI), and the interaction of amino acid bonds and residues formed with the receptor. The affinity of the bond plays a role in describing how strong the interaction between the ligand bonds is with the active side of the target receptor. Free energy (ΔG) is an indispensable component in the affinity interaction between ligands and target receptors. The smaller the free energy value (ΔG), the more stable the interaction between the ligand and the receptor [23], [24]. Based on this, the ability of the four test compound to inhibit the enzyme exo-1,3-β-glukanase is close to the comparator, making it relevant to become a new drug candidate.

**Table 3**. Free Energy Results and Inhibition Constants Comparative Ligands (*) and Test Compounds

| Compound Name | Free energy (kcal/mol) | Constant Inhibitions (nM) |
|---|---|---|
| Ibrexafungerp (*) | -9.36 | 137.06 nM |
| Beta-amyrin | -8.24 | 908.46 nM |
| Lupeol | -8.19 | 994.44 nM |
| Ethyl-iso Allocholate | -7.66 | 2.44 μM |
| Magnolol | -7.2 | 5.25 μM |
| Methyl ellagic acid | -6.92 | 8.46 μM |
| Quinizarin | -6.6 | 14.44 μM |
| 3', 4', 5, 7-Tetrahydroxy-3,6,8-trimethoxyflavone | -6.55 | 15.84 μM |
| Catechin | -6.48 | 17.80 μM |
| Dasycarpidan-1-methanol-acetate | -6.24 | 26.61 μM |
| Xanthotoxin | -6.04 | 37.54 μM |
| Synephrine | -6.03 | 37.71 μM |
| Hygrene | -5.97 | 41.97 μM |
| Scopoletin | -5.72 | 63.93 μM |
| Coumarin | -5.54 | 86.59 μM |
| Phytol | -5.52 | 89.44 μM |
| Metacetamol | -5.11 | 181.10 μM |
| Coumaryl alcohol | -4.91 | 252.84 μM |
| Linolenic acid | -4.9 | 257.09 μM |
| Myrcene | -4.48 | 516.46 μM |
| Coumaric acid | -4.43 | 565.00 μM |
| Catechol | -4.37 | 623.55 μM |
| n-Hexadecanoic acid | -4.33 | 665.83 μM |
| Caffeoyl alcohol | -4.28 | 726.95 μM |
| Octanal | -4 | 1.17 mM |
| Oleic acid | -3.99 | 1.19 mM |
| Syringic acid | -3.9 | 1.38 mM |
| Glucuronic acid | -3.36 | 3.44 mM |
| 3-O-methyl-Glucose | -2.34 | 19.32 mM |

Based on the data in Table 1, the visualization of docking results was obtained, ibrexafungerp interacted with receptors bound to the amino acids TYR255, HIS253, GLU192, TRP277 (figure 1). Beta-amyrin interacts with receptors that bind to the amino acids GLY143, ASP151, ARG309 (figure 2). Lupeol interacts with receptors that bind to the amino acids PHE144, PHE258 (figure 3). Ethyl-iso allocholate interacts with receptors that bind to the amino acids ARG265, GLU262, ARG312 (figure 4). Magnolol interacts with receptors that bind to the amino acid GLU192, LEU304 (figure 5). The amino acid residues formed from the validation process are GLU27, TYR29, HIS135, ASN191, TYR255, GLU192. Based on the literature, the active side of the Exo-1,3 β-glucanase receptor includes

the following amino acids: ARG92, HIS135, ASN191, GLU192, HIS253, TYR255, GLU292, TRP363. Apart from the amino acids above, there are also ligands that can have potential but are allosteric. Allosteric is the condition of a ligand not binding to an amino acid that is the active site of a receptor but allows the compound to become a new drug candidate [25], [26], [27].

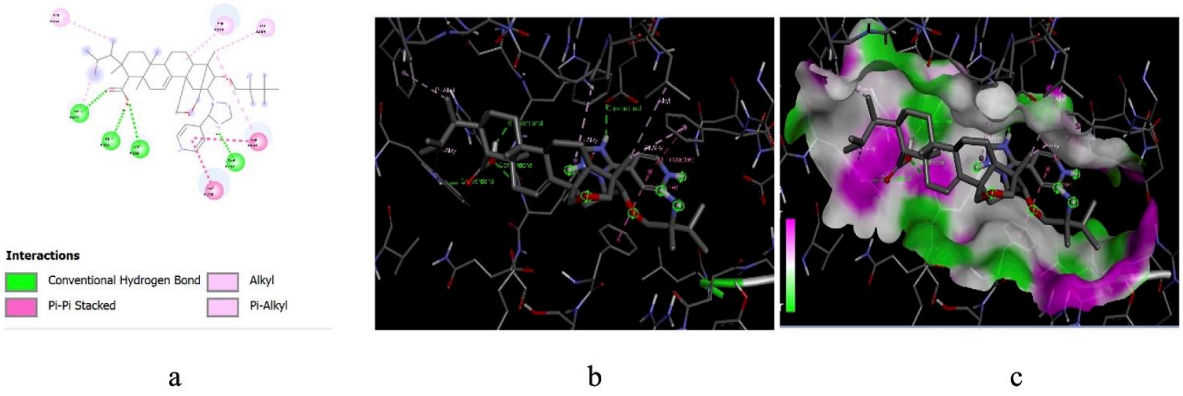



**Figure 1.** In silico analysis of the 2D (a), 3D (b), 3D HBond interaction (c) of ibrexafugerp with the active site of target protein

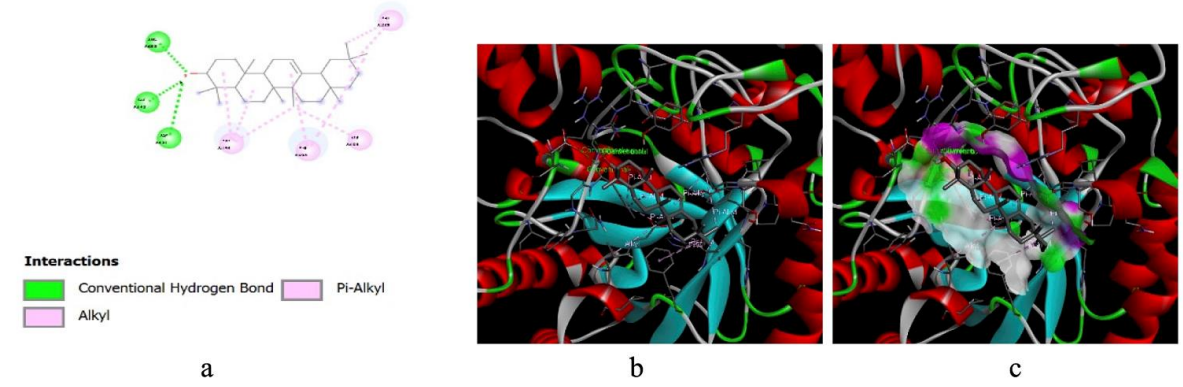



**Figure 2.** In silico analysis of the 2D (a), 3D (b), 3D HBond interaction (c) of β-amyrin with the active site of target protein

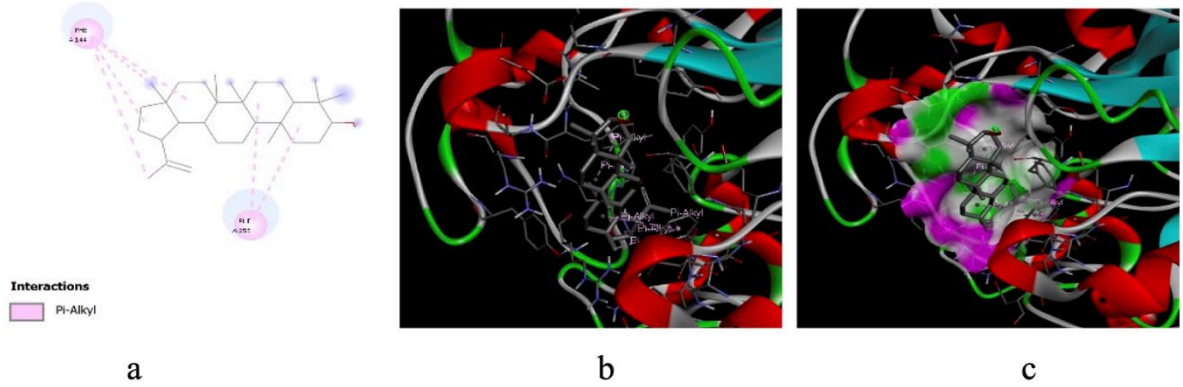



**Figure 3.** In silico analysis of the 2D (a), 3D (b), 3D HBond interaction (c) of lupeol with the active site of target protein

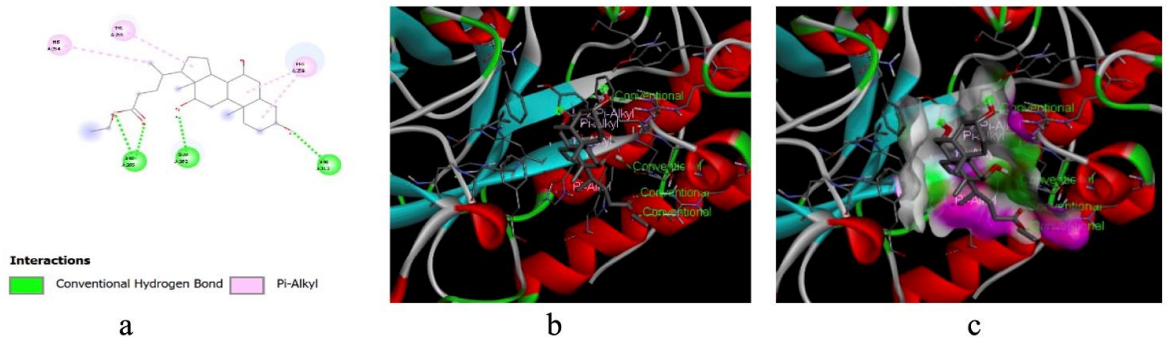



**Figure 4.** In silico analysis of the 2D (a), 3D (b), 3D HBond interaction (c) of ethyl-iso allocholate with the active site of target protein

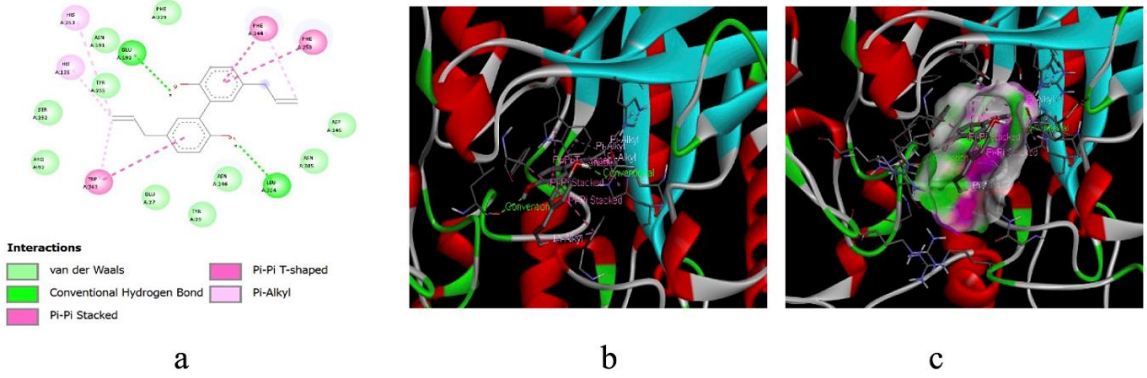



**Figure 5.** In silico analysis of the 2D (a), 3D (b), 3D HBond interaction (c) of magnolol with the active site of target protein

*3.3. Prediction of Physicochemical Parameters*

Based on the results of the Lipinski's rule of five test that has been carried out, the results were obtained that out of 4 test compounds, 2 compounds did not meet the requirements of Lipinski's 5 rules, namely β-amyrin and Lupeol. β-amyrin and Lupeol are triterpenoid compounds with a fairly large and complex chemical structure. Its molecular weight often exceeds the maximum limit of 500 Daltons required by Lipinski. Heavy molecules tend to be difficult to absorb efficiently in the intestines. Due to their hydrocarbon-dominant (non-polar) structure, β-amyrin and Lupeol have high LogP values (more than 5), meaning that these molecules are highly lipophilic (fat-soluble) and less soluble in water. This can inhibit solubility and absorption in the digestive tract [28], [29]. Lipinski's Rule of five is often used as a parameter to predict new drug candidate compounds that can be used as an oral preparation. Lipinski rules that new drug candidate compounds should not have a molecular weight of more than 500 Da, a lipophility value (log P) should not be more than 5, a hydrogen donor should be less than 5, and a hydrogen acceptor should not exceed 10 [30]. The results of physicochemical parameters can be seen in Table 4.

**Table 4.** Results of physicochemical parameters

| Compounds | Parameter Lipinski's Rule of Five | | | |
|---|---|---|---|---|
| | Molecular weight | Log P | Hydrogen Acceptor | Hydrogen Donor |
| Ibrexafungerp | 730.051 | 8.6184 | 8 | 2 |
| β-amyrin | 426.00 | 8.168903 | 1 | 1 |
| Lupeol | 426.00 | 8.024803 | 1 | 1 |
| Ethyl-iso allocholate | 436.00 | 3.927198 | 5 | 3 |
| Magnolol | 266.00 | 4.221799 | 2 | 2 |

*3.4. ADMET Prediction*

Testing of the absorption parameters of the test compound that has good penetration ability to the intestinal membrane based on the Caco-2 unit because the value is > 0.90 namely β-amyrin, lupeol, Ethyl-isoallocholate, and Magnolol. All four compounds that have good penetration can be well absorbed in the human intestinal [31]. Caco-2 permeability is widely used as an early indicator of a compound's penetration through the transcellular pathway. This value supports high human intestinal absorption results, indicating that the compound has good absorption potential in the gastrointestinal tract. A log Kp value between -2.5 and -4.0 indicates that the compound still has the potential to penetrate the skin, although not as strongly as lipophilic compounds [32].

Based on the data obtained, from 4 test compounds, 3 test compounds were found that were well distributed because they had VDss values in the range of -0.15 to 0.45 or higher, namely β-amyrin, Magnolol and Lupeol. From the results of the unit fraction unbound of 4 test compounds, 1 test compound was obtained which had a value of > 0.1, namely. Lupeol. The results of the research from 4 test compounds on the BBB permeability unit, the four compounds have the ability to penetrate the blood barrier of the brain but 2 of them have high penetration ability, namely Ethyl-isoallocholate and Lupeol. For the results of CNS permeability, from 4 test compounds, data was obtained that there were 3 compounds that had high penetration ability, namely β-amyrin, Magnolol, and Lupeol because they had a logPS value of >-2. The VDss value indicates the theoretical volume at which the compound must be distributed to achieve a uniform concentration throughout the body. Higher VDss values in log units (L/kg) indicate a wide distribution to the network. The VDss log value > 0.45 is generally considered a broad distribution [33].

Fraction unbound (fu) refers to the fraction of compounds that are not bound to plasma proteins and are pharmacologically active. A high fu value indicates more compounds are available to penetrate the membrane and interact with biological targets with a fu value of ≤ 0.1 indicates that the compound bound to proteins is about more than 90% and if fu ≥ 0.9 then plasma protein binding is negligible [34].

The ability of compounds to cross the Blood-Brain Barrier (BBB) is also analyzed through the BB (Brain-to-Blood ratio) log value. A log BB value of > 0.3 indicates high penetration into the brain, while < -1 indicates very low penetration [35]. CNS permeability values indicate the ability of the compound to penetrate the network of the central nervous system in general. This parameter is reported as a PS (permeability-surface area product) log. A PS log value of > -2 indicates high penetration, while a value of < -3 indicates very low penetration [36].

Based on the results of the study of metabolic parameters, most compounds can be CYP2D6 and CYP3A4 substrates and not be CYP2D6 and CYP3A4 inhibitors. CYP2D6 aims to activate the prodrug when the compound binds to a receptor while CYP3A4 plays a role in the drug elimination process by being influenced by enzymes [37]. The test compounds were analyzed against several major isoforms of the CYP450 enzyme, namely CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2, both as substrates and inhibitors. If a compound is a substrate of an enzyme, then the compound will be metabolized by that enzyme, whereas as an inhibitor, the compound has the potential to inhibit enzyme activity and affect the metabolism of other compounds that depend on the same pathway [38]. In addition, the compound's status as a non-inhibitor of the CYP enzyme also indicates that the compound will not cause the accumulation or increase in levels of other drugs metabolized through the same pathway. This is a plus in terms of safety of long-term use and combination therapy [39].

The results of the research from 4 test compounds, in the excretion parameters of the total clearance value, data was obtained that all of the test compounds have the ability to be excreted slowly by the body. Meanwhile, in the Renal OCT2 unit, data was obtained that the test compound could not be actively excreted through the kidneys [40].

Testing on the toxicity parameters of the 4 compounds tested, it was found that all test compounds did not cause mutagenic. Of the 4 compounds tested, all test compounds could not cause hepatotoxicity. Furthermore, out of 4 test compounds, 1 compound was found that causes allergic skin reactions, namely Magnolol. Ames toxicity is used to predict the mutagenic potential of a compound based on Ames' test with Salmonella typhimurium. Oral rat acute toxicity ($LD_{50}$) describes

an acute dose that causes death in 50% of the rat population after oral administration. This value is usually expressed in log mol/kg. The higher the $LD_{50}$ value, the lower the acute toxicity. This value provides an early indication of the safety of the compound against single exposure in large doses [41].

Hepatotoxicity, which is the potential of compounds to cause liver damage, was also analyzed. This result is important considering that the liver is the main organ of drug metabolism, and liver damage [42]. Skin sensitisation is used to assess the potential for compounds to cause allergic reactions in the skin. It is important to consider the safety of using the compound in topical preparations as well as the risk of accidental exposure [43]. Total clearance (CLtot) refers to the volume of plasma cleared of compounds per unit of time, covering the entire elimination pathway such as kidneys, liver, and others. This value is usually expressed in log form (mL/min/kg). The higher the clearance value, the faster the compound is eliminated from the body [44]. The results of the ADMET prediction test of the four compounds can be seen in Table 5. The study's limitation is the absence of in vitro or in vivo experiments concerning the test substances.

**Table 5.** The results of the ADMET prediction testers of the four compounds

| Parameters of ADMET | Ibrexafungerp | β-amyrin | Lupeol | Ethyl-iso allocholate | Magnolol |
|---|---|---|---|---|---|
| Water Solubility | -2.972 | -7.522 | -5.861 | -4.734 | -4.729 |
| Caco2 Permeability | 0.703 | 1.352 | 1.226 | 1.032 | 1.499 |
| Intestinal absorption | 90.539 | 93.29 | 95.782 | 97.702 | 92.473 |
| Skin Permeability | -2.735 | -2.898 | -2.744 | -4.057 | -2.554 |
| VDss | -0.691 | 1.122 | 0 | -0.17 | -0.01 |
| BBB Permeability | -0.921 | 0.184 | 0.726 | 0.796 | 0.233 |
| Fraction unbound | 0.071 | 0 | 0.134 | 0.076 | 0.082 |
| CYP3A4 Substrate | Yes | Yes | Yes | Yes | No |
| CYP 2C19 Inhibitor | No | No | No | No | Yes |
| CYP2C9 Inhibitor | No | No | No | No | No |
| CYP3A4 Inhibitor | No | No | No | No | No |
| Total Clearence | -0.864 | -0.08 | 0.153 | 0.748 | 0.426 |
| Renal OCT2 Substrate | No | No | No | No | No |
| AMES Toxicity | No | No | No | No | No |
| Oral Rat Acute Toxicity | 2.603 | 2.139 | 2.47 | 2.045 | 2.068 |
| Hepatotoxicity | Yes | No | No | No | No |
| Skin Sensitisation | No | No | No | No | No |

## 4. CONCLUSION

The results of the molecular docking test of 28 secondary metabolite compounds in black mangrove plants (*Rhizopora mucronata* L.), there are 4 compounds that have free energy (ΔG) and KI that are close to the most optimal comparator used in this study, namely Ethyl-isoallocholate, β-amyrin, Magnolol, and Lupeol with β-amyrin which has free energy and the smallest KI which is -8.24 kcal/mol and 908.46 nM which shows good affinity to Exo-1 receptors, 3 β-Glucanase. Based on the results of ADMET prediction testing from 4 molecular docking test compounds, the four compounds have quite good penetration ability on the skin. So that the four compounds have the potential to be developed as new drug candidates to inhibit Exo-1,3 β-Glucanase in *Candida albicans.*

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