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Molecular docking analysis of *Cinnamomum zeylanicum* phytochemicals against Secreted Aspartyl Proteinase 4–6 of *Candida albicans* as anti-candidiasis oral

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ABSTRACT

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Candida albicans is a polymorphic human microflora species, which caused a candidiasis. This disease frequently occurred in immunocompromised patients with considerable medical outcomes due to the damage from its infections. Secreted Aspartic Proteinase (SAP) 4–6 regulated the virulence of *C. albicans*. Thus, inhibiting those proteinases may be useful to obtain a better prognosis. On the other hand, *Cinnamomum zeylanicum* reported to have anti-candidiasis. However, the mechanism of action on the anti-candidiasis activity remains unclear. This study will explain the possible mechanism of anti-candidiasis from the bioactives of *C. zeylanicum* through SAP 4–6 inhibition. A computational analysis was employed by molecular docking coupled with molecular dynamics simulation to comprehend the interaction among *C. zeylanicum* bioactives to SAP 4–6. Positive docking outcomes were observed, with Cinnamaldehyde, Pyrantel Hydrochloride, and Hexadecenoic Acid became promising binding affinity against SAP 4–6. However, those compounds interacted with different residues of each proteinase. Only Hexadecenoic Acid bound to the catalytic residues of SAP5-6. Molecular dynamics simulated the stable binding of Hexadecenoic Acid to the SAP5-6. Not only has stable structural integrity, the binding of Hexadecenoic Acid also showed minimum alterations on the structural stability of SAP5-6, which suggested a stable inhibitory activity. The stable binding of Hexadecenoic Acid also displayed by the prominent number of hydrogen bond and the free-binding energy simulations. In conclusion, the anti-candidiasis activity of *C. zeylanicum* may take place in the SAP5-6 inhibition, mainly by Hexadecenoic Acid.

1. Introduction

Candida albicans are a species of opportunistic pathogenic yeast [1,2] found in many ecological niches across the globe. These fungi are frequently ranked first for their propensity to cause nosocomial infections [3]. Due to their major adaptive evolutionary biochemical mechanism, they also persist as endophytic fungi in a number of plants and as gut microbiota in humans [2,4]. These fungi can induce irreversible pathogenic effects in immunocompromised host organisms, such as candidiasis oral [1], where they exist as commensals that rely on the host for shelter and sustenance but do not cause damage to the host

[2]. This opportunistic nature cannot exist without the support of its virulence component, the Secreted Aspartyl Proteinase (SAP) protein [1,5], in addition to morphological alterations (dimorphism) and adhesion [6]. Secreted Aspartyl Proteinase (SAP) is a marker for the formation of *C. albicans* hyphae which indicates the host has been infected.

This protein SAP encodes the multigene family sequentially from 1 to 10 (SAP 1–10) and has varying expression levels [1,6]. Therefore, it is impossible to separate the infection process produced by *C. albicans* from the function of this protein, which encodes the SAP 1–10 gene. It is known that the SAP 4–6 gene plays a significant role in oral candidiasis

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and hyphal development during infection [1,5]. This is due to the expression of the SAP 4–6 gene during hyphal development in oral candidiasis [1,7]. The protein SAP 5 of the SAP family is more likely to produce pathogenicity [8]. The SAP protein is responsible for digesting molecules to acquire nutrients, breaking the host cell membrane for invasion and tissue damage, and attacking the immune system to evade antimicrobial action from the host organism [9]. The active core of the pathogenic protein SAP can be blocked by phytochemicals derived from plants. The phytochemicals are the secondary metabolites of plants that are not directly engaged in the plant's growth and development, but instead offer a variety of medical qualities, such as antibacterial, anti-cancer, antitoxic, and anti-diabetic capabilities [10]. Therefore, SAP 4–6 is a target in treating infections caused by *C. albicans* using phytochemical compounds.

By competing with its substrate, phytochemicals from plants have the potential to block the active site of the enzyme, so neutralizing the effects of the virulence-causing enzyme [2]. Several plant extracts, including methanol in hydroalcoholic and ethyl acetate methanol leaf extracts from *Schinus terebinthifolius*, have demonstrated the ability to suppress the formation of *Candida* biofilm [2,11]. Alkaloids, terpenoids, phenols, and anthraquinones were identified by thin layer chromatography [11]. *Croton urucurana* stem bark extracts derived from ethyl-acetate and methanol prevent *C. albicans* biofilm development [2,10]. Similarly, ethyl-acetate extracts of *Syzygium aromaticum* flower buds have the capacity to suppress *Candida* biofilms [10,12]. In addition to crude extracts, plant phytochemicals such as terpenoids, alkaloids, and flavonoids have been found to suppress the biofilm formation of *C. albicans* [10]. Baicalein reduced around 70 % of *C. albicans* biofilm on prosthetic surfaces [13]. In numerous investigations, phytochemicals such as curcumin, sesquiterpenes, and purpurin inhibited *Candida* biofilm effectively [14–16]. The phytochemical compounds can inhibit the formation of *C. albicans* biofilm, especially alkaloids and terpenoids.

Cinnamomum zeylanicum is a member of the family Lauraceae, which has long been used as a therapeutic agent in various cultures and with a long history [17]. Various parts of the body of *C. zeylanicum*, including flower, fruit bark, leaves, and roots, have been known to have medicinal properties and are widely used as drugs for gynecology, urinary tract problems, respiratory problems, diabetes, acne, and digestive diseases [18,19]. *C. zeylanicum* has also been known to have potential as an antimicrobial that can inhibit the growth of various bacteria and fungi [19–21]. Oro et al., (2015) [20] stated that *C. zeylanicum* essential oil (0.0313–64 µg/mL) could inhibit the growth of *Candida* strain by 93.3 %. Alizadeh Behbahani et al., (2020) [22] reported that *C. zeylanicum* bark essential oil could inhibit the growth of pathogenic microbes such as *Staphylococcus aureus*. *C. zeylanicum* contained phytochemical compounds such as (E)-cinnamaldehyde (71.50 %), linalool (7.00 %), carvophyllene (6.40 %), eucalyptol (5.40 %), and eugenol (4.60 %) [22]. Thus, *C. zeylanicum* can be developed as a natural antifungal drug for treating oral candidiasis and OPC in COVID19 patients. The purpose of this in-silico study was to examine the drug-likeness and molecular docking of natural plant phytochemicals against the active site of *C. albicans* SAP 4–6 protein. This effort would be an initiative to create *C. zeylanicum* phytochemicals as potential treatment for *Candida albicans* with known mechanism of action through SAP inhibition.

2. Materials and methods

2.1. Preparation of protein molecules and compounds obtained

The structure of SAP 4–6 was retrieved from Uniprot database. Only SAP 5 has a structure from experimental elucidation (PDB ID = 2QZX), while SAP 4 and 6 was obtained from AlphaFold-modeled structure with identity code AF-Q5A8N2-F1 and AF-Q5AC08-F1, respectively. The structure of the compounds were obtained from the PubChem database with the following identities: Cyclopentane (CID: 7296), Cinnamaldehyde (CID: 637511), Hexadecenoic Acid (CID: 13105359), Eugenol

Table 1

Position of grid box in docking process between *C. zeylanicum* compound and SAP 4–6.

Proteins	Centre			Dimensions		
	X	Y	Z	X	Y	Z
SAP 4	-4.2031	-6.2199	-0.9820	22.1452	22.3045	26.7720
SAP 5	37.1947	9.2264	63.1753	20.8892	23.7266	25.4676
SAP 6	3.6349	9.4856	1.3570	26.2490	25.3176	26.0087

(CID: 3314) and Pyrantel Hydrochloride (CID: 6365307). In addition, Pepstatin was used as a standard for SAP inhibitor, which was extracted from SAP 5's structure. The compounds went to energy minimization and set as ligand prior the docking process. Also, the structure of SAP was prepared by deleting the unwanted molecules and waters then set as rigid macromolecules for the docking step.

2.2. Active site prediction

The enzyme's catalytic site is used to direct the grid box during docking. The residues of the catalytic site of SAP5 was identified based on previous research [23]. In contrast, the catalytic site of SAP 4 and 6 were predicted using COACH-D [24].

2.3. Molecular docking

AutoDock Vina in PyRx 0.9.5. software [25,26] was employed to calculate the binding energy and define the binding pose of each compound to the respective proteinase. The SAPs was set as rigid receptors, while the compounds were set as flexible ligands [27]. Specific docking was employed with grid box setting as shown in Table 1.

2.4. Molecular dynamics simulation

Simulations were carried out using YASARA version 21 [28] with AMBER14 forcefield [29]. The simulation parameters are as follows: pH 5.0; 0.9 % NaCl concentration; 0.997 water density; 1 atm pressure; 20 ns running time; and 310°K temperature with cubic grid shape. The calculation of the value of bond energy stability or molecular mechanics energies combined with the Poisson-Boltzmann (MMPBSA) [30] was carried out using the Poisson-Boltzmann (PBS) method on macros md_analyzebindingenergy.mcr from YASARA. The equation for calculating the free bond energy is as follows:

$$\Delta E_{\text{binding}} = (\Delta EP_{\text{receptor}} + \Delta ES_{\text{receptor}} + \Delta EP_{\text{ligand}} + \Delta ES_{\text{ligand}}) - (\Delta EP_{\text{complex}} + \Delta ES_{\text{complex}})$$

where E is energy, EP is potential energy, and ES is solvation energy.

2.5. Results analysis

The docking conformation with the lowest Root-Mean-Square Deviation (RMSD) was determined as the ideal conformation with the lowest bond energy value. Those conformations then analyzed for protein-compound interaction clarity using Discovery Studio 2019. On the other hand, the values of Radius of Gyration (R_g) and Root-Mean Square Fluctuation (RMSF) were used to determine the stability of protein structure during the molecular simulations, while the stability of the ligand structure was defined based on the Root-Mean Square Deviation (RMSD) value of the ligand atomic position. The stability of the interaction between the proteins and the ligands was evaluated based on the number of hydrogen bonds and the free binding energy dynamics based on the MMPBSA calculations during the simulation period.

Table 2
Predicted arrangement of amino acid residues acting as catalytic sites of SAP4 and 6 proteins according to the COACH-D program.

Proteins	Predicted Catalytic Sites
SAP4	ILE87, THR88, ILE105, ASP107, GLY109, SER110, LYS158, TYR159, ALA160, ASP161, ALA194, HIS195, ILE198, THR269, LEU291, ASP293, GLY295, THR296, THR297, ILE298, TYR300, ASP378, ILE380
SAP6	ILE87, ILE88, THR89, ILE106, ASP108, GLY110, SER111, ILE158, LYS159, TYR160, ALA161, ALA195, ILE199, ASN207, THR270, LEU292, ASP294, GLY296, THR297, THR298, TYR301

3. Results

3.1. SAP 4 and SAP 6 active side prediction

Based on the prediction results with COACH-D, the following is the prediction of the active side of each SAP 4 and SAP 6 (Table 2). The residue number represents the amino acid sequence based on the amino acid sequence of each protein. Based on these predictions, it will direct the position of the grid box during molecular docking to the catalytic side.

3.2. Binding energy of *C. Zeylanicum* compound with SAP protein

The binding energy of the docking results is shown in Table 3. Pepstatin as control has the lowest energy value for SAP 5 and SAP 6

Table 3
The binding energy of each compound of *C. zeylanicum* and Pepstatin to SAP 4–6 protein is based on the scoring results with AutoDock Vina.

Proteins	Binding Energy (kcal/mol)					
	Cinnamal-dehyde	Cyclopentane	Pyrantel Hydrochloride	Eugenol	Hexadecenoic Acid	Pepstatin
SAP4	-5.9	-4.4	-5.3	-5.8	-6.4	-4.8
SAP5	-5.6	-4.0	-5.9	-5.7	-5.4	-8.8
SAP6	-5.4	-4.2	-6.2	-5.5	-5.8	-8.4

proteins but not for SAP 4. Each of the compounds analyzed prefers interacting with the three target proteins with the lowest energy values. In SAP 4, Eugenol has the lowest energy value, which indicates a high probability of acting as an inhibitor of SAP 4. In addition, SAP 5 and SAP 6, each filled with Pyrantel Hydrochloride, is the compound with the lowest bond energy among all analyzed compounds. However, these compounds still have energy values that are not lower than Pepstatin. Determination of the inhibitory activity of a compound cannot be determined based on the value of its bond energy alone, so further analysis is needed regarding the type of bond or chemical interaction between the structure of the compound and several amino acid residues of the target protein.

Table 4
List of SAP 4 catalytic residues interacting with the analyzed compounds.

Compounds	No. Residue
Cinnamaldehyde	ILE105, ASP107, GLY109, SER110, TYR159, ASP161, ALA194, ILE198, ASP293, GLY295
Cyclopentane	ILE105, ASP107, GLY109, SER110, TYR159, ASP161, ILE198, GLY295
Pyrantel Hydrochloride	ILE87, THR88, ILE105, ASP161, ALA194, HIS195, ILE198
Eugenol	ILE87, THR88, ILE105, ASP161, ALA194, HIS195, ILE198
Hexadecenoic Acid	ILE87, THR88, ILE105, ASP107, GLY109, SER110, TYR159, ALA194, HIS195, ILE198, ASP293, GLY295, THR296
Pepstatin	ALA160, ASP378

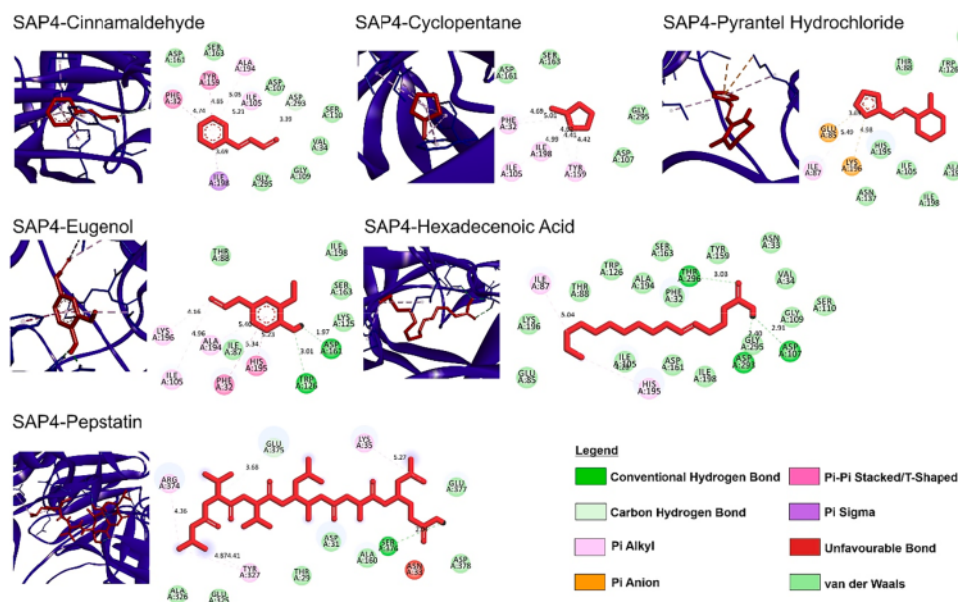


Fig. 1. The binding pose of *C. zeylanicum* compounds with SAP 4 and the schematic visualization of interactions with SAP 4 residues using a 2-dimensional interaction diagram.

Table 5
List of SAP5 catalytic residues interacting with the analyzed compounds.

Compounds	No. Residue
Cinnamaldehyde	TYR84, ASP86, SER88, SER118, ALA119, ARG120, ILE123
Cyclopentane	TYR84, ASP86, SER88, ALA119, ARG120, ILE123
Pyrantel Hydrochloride	GLY34, SER35, TYR84, GLY85, ASP86, ALA119, ARG120, ILE123, THR221, ILE305
Eugenol	ILE12, ASP86, SER88, SER118, ALA119, ARG120, ILE123, GLY220
Hexadecenoic Acid	TYR84, GLY85, ASP86, SER88, ALA119, ARG120, ILE123, GLY220, THR221, THR222
Pepstatin	ILE12, GLY34, SER35, ILE82, LYS83, TYR84, GLY85, ASP86, SER88, ARG120, LEU216, GLY220, THR221, THR222, ILE223, TYR225

3.3. Compound interaction with SAP4

Several compounds have the potential to act as inhibitors of SAP 4 based on their interaction position with the catalytic residue. Hexadecenoic Acid is the compound with the best potential as a SAP 4 inhibitor because it has the highest number of interactions with SAP 4 catalytic residues, followed by Cinnamaldehyde (Fig. 1 and Table 4). Several chemical interactions were also formed, including several hydrogen bonds in Hexadecenoic Acid and hydrophobic bonds in Cinnamaldehyde (Fig. 1). This potential is also supported by the lower bond energy values than other compounds, including pepstatin (Table 3).

3.4. Compound interaction with SAP 5

Although *C.zeylanicum* compounds have bond energy values not lower than Pepstatin, some combinations can interact with some catalytic residues of SAP 5. Among these compounds, Hexadecenoic Acid is the compound with the most interactions on catalytic residues compared to other compounds, followed by Pyrantel Hydrochloride. With the lowest bond energy values, Pepstatin has the most interactions on the

catalytic side (Table 5). Pepstatin has many hydrogen and hydrophobic bonds, strengthened by van der Waals interactions. On the other hand, Pyrantel Hydrochloride also has one hydrogen bond at residue no. 34, supported by several hydrophobic bonds and van der Waals interactions, while Hexadecenoic Acid has two hydrogen bonds at residue no. 85 and 86 with hydrophobic bonds help at residue no. 30 and 123 and some van der Waals interactions (Fig. 2).

3.5. Compound interaction with SAP 6

In the results of docking with SAP 6, Pyrantel Hydrochloride again had the highest number of interactions with the protein catalytic residue of SAP 6, followed by Cinnamaldehyde. With the lowest bond energy value, Pepstatin again had the highest number of interactions compared to compounds from *C. zeylanicum* (Table 6). Pyrantel Hydrochloride has three carbon-hydrogen bonds at residue n^o 108, 164, and 294 supported by several hydrophobic bonds and van der Waals interactions. The low value of bond energy in Pepstatin occurs due to a large number of interactions of pepstatin atoms with several SAP6 catalytic residues through several strong bonds, such as hydrogen bonds and hydrophobicity (Fig. 3).

Table 6
List of SAP 6 catalytic residues interacting with the analyzed compounds.

Compounds	No. Residue
Cinnamaldehyde	ALA161, GLY296, THR297, THR298, TYR301
Cyclopentane	ALA161, THR297, TYR301
Pyrantel Hydrochloride	ASP108, TYR160, ALA161, ILE199, ASP294, GLY296, THR297, TYR301
Eugenol	ILE88
Hexadecenoic Acid	ILE88
Pepstatin	ILE88, THR89, ILE106, ASP108, TYR160, ALA161, ALA195, ILE199, GLY296, THR297, THR298, ILE299, TYR301

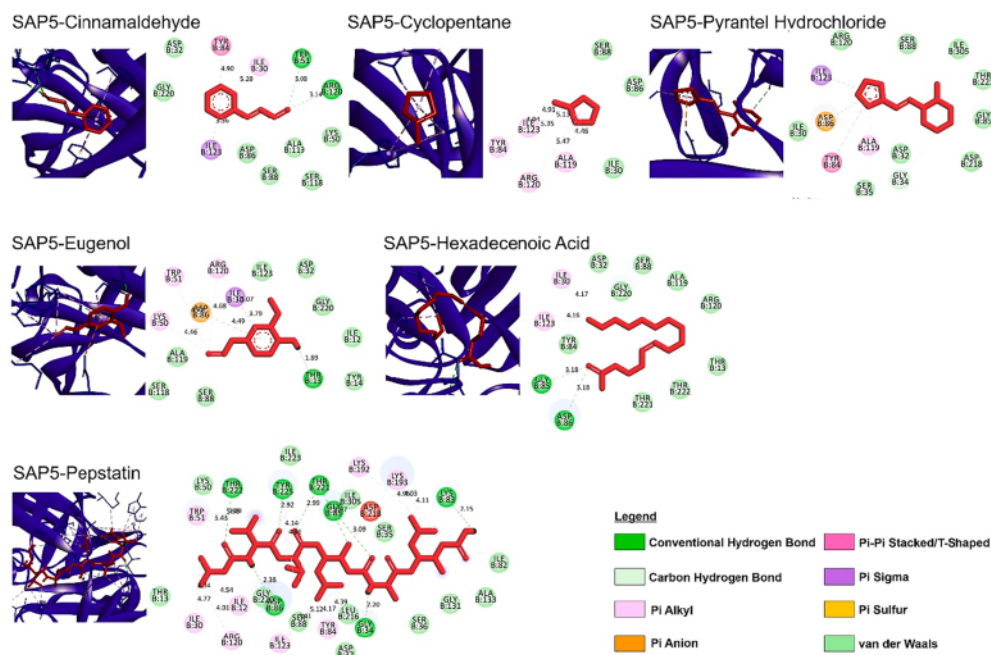


Fig. 2. The binding pose of *C. zeylanicum* compounds with SAP 5 and the schematic visualization of interactions with SAP 5 residues using a 2-dimensional interaction diagram.

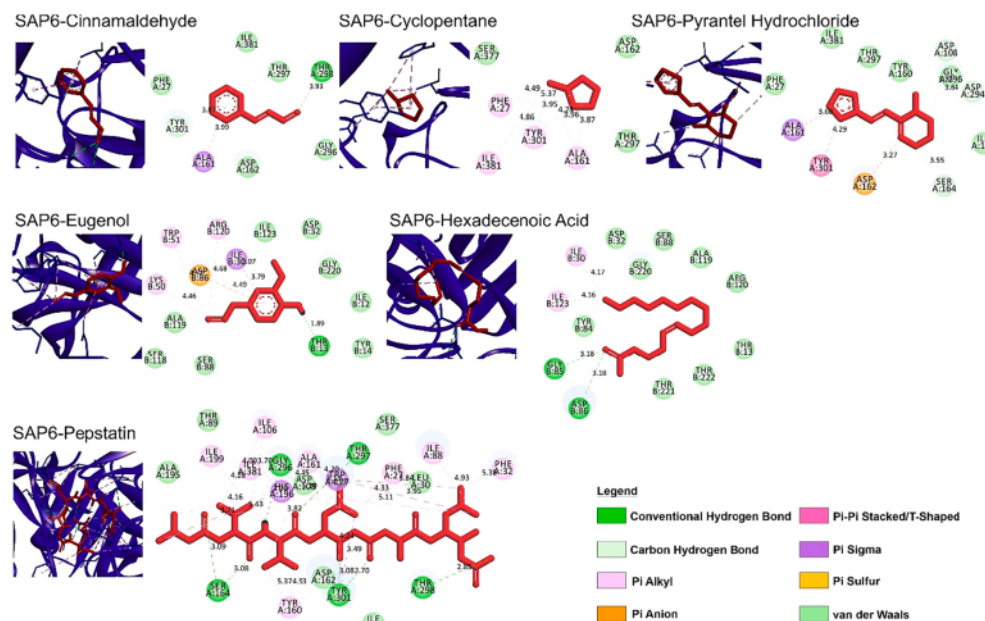


Fig. 3. The binding pose of *C. zeylanicum* compounds with SAP 6 and the schematic visualization of interactions with SAP 6 residues using a 2-dimensional interaction diagram.

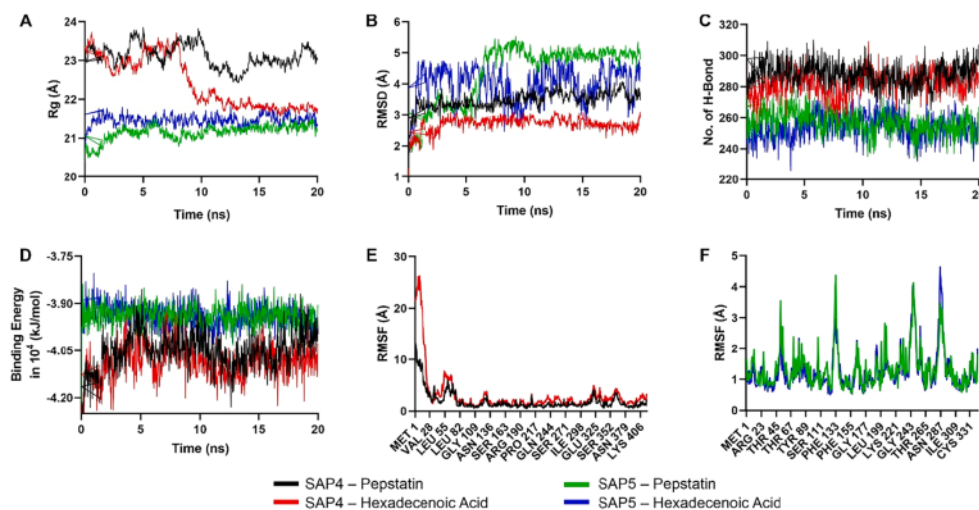


Fig. 4. Stability of protein structure, ligands, and their interactions at optimum physiological conditions of SAP. Respectively, the Rg value describes the structural integrity of the protein (A), the RMSD ligand, which indicates the stability of the ligand structure (B), the number of hydrogen bonds (C) and the bond energy value (D), which means the strength of the protein-ligand interaction, and the RMSF value. On each residue in SAP 4 (E) and SAP 5 (F) after interacting with Pepstatin and 5-Hexadecenoic Acid.

3.6. Complex stability based on molecular dynamics simulation

Molecular dynamics simulation results show that SAP 4 and SAP 5 complexes bound to Hexadecenoic Acid have **33** per protein structure integrity than Pepstatin, indicated by a smaller Radius of Gyration (Rg) until the end of the simulation (Fig. 4A). In addition, the structure of Hexadecenoic Acid also has a lower atomic fluctuation value with a maximum value below the fluctuation of the RMSD Pepstatin value for both SAP 4 and SAP 5 (Fig. 4B). The number of hydrogen bonds also

showed a stable interaction between Hexadecenoic Acid and SAP protein when compared to fluctuations in the number of hydrogen bonds of SAP with Pepstatin (Fig. 4C). The stability of **31** Hexadecenoic Acid interaction with SAP4 and SAP5 showed from the Binding Energy value based on the MMPBSA analysis. The binding energy value also indicates a more robust and stable Hexadecenoic Acid interaction tendency towards SAP5 compared to SAP4 (Fig. 4D and Table 7). At the residue level, the fluctuations that occur have similar values between the residues of SAP 4 and SAP 5 that bind to Pepstatin, although SAP 4 shows an

Table 7
Calculation of free binding energies of SAP 4 and SAP 5 with Pepstatin and Hexadecenoic Acid.

		SAP 4 – Pepstatin	SAP 4 – Hexadecenoic Acid	SAP 5 – Pepstatin	SAP 5 – Hexadecenoic Acid
$\Delta E_{\text{binding}}$ (in 10^4 kJ/mol)	Binding	-4.056 ± 0.096	-4.089 ± 0.090	-3.939 ± 0.055	-3.942 ± 0.057
	Potential Receptor	-1.470 ± 0.092	-1.457 ± 0.110	-1.690 ± 0.066	-1.637 ± 0.064
	Solvation Receptor	-2.614 ± 0.071	-2.630 ± 0.083	-2.302 ± 0.058	-2.321 ± 0.053
	Potential Ligand	-1.440 ± 0.091	-1.442 ± 0.109	-1.644 ± 0.067	-1.625 ± 0.063
	Solvation Ligand	-2.619 ± 0.071	-2.650 ± 0.082	-2.295 ± 0.058	-2.317 ± 0.050
	Potential Complex	-1.470 ± 0.092	-1.457 ± 0.110	-1.690 ± 0.066	-1.637 ± 0.064
	Solvation Complex	-2.617 ± 0.070	-2.632 ± 0.082	-2.302 ± 0.059	-2.321 ± 0.053

Notes: Each value was presented in mean ± standard deviation.

unstable part of the C-terminal residue (Fig. 4E and F). Hexadecenoic Acid is a compound with high bioactivity potential to act as an inhibitor of SAP 4 and SAP 5 to prevent the development of *C. albicans* from reducing the severity of candidiasis.

4. Discussion

Globally, more than 7.5 million people are plagued by invasive Candidiasis, with a mortality rate of roughly 40 % [2]. The unfavorable side effects, ineffectiveness, and rapid evolution of fungus resistance have increased the demand for novel antifungals [2,31]. The mechanism of action of plant phenolic compounds with antifungal activity against *C. albicans* is currently poorly understood [2,32,33]. SAPs are utilized to destroy foreign tissue and elude the host's immune system [1,34]. Strains of *C. albicans* lacking SAP1, SAP2, and SAP3 are significantly less virulent and caused negligible harm to an in vitro model [23,35]. 7-hydroxycalamenene and hydroxylated sesquiterpene derived from *Croton cajucara* suppress SAP [36]. The ethanol extract of *Lycopodium cernuum* contains triterpene chemicals and inhibits aspartic proteases produced by *Candida albicans* [37].

AutoDock Vina was utilized to determine the binding affinity of five *C. zeylanicum* compounds to determine the differences between candidates in molecular interactions, such as hydrogen bonds and hydrophobic contact, with residues inside the protein target [38,39]. In other words, conducted virtual screening to choose the best candidate. We selected the program due to its usability, processing speed, and ability to forecast binding model bindings accurately. Due to various limitations, such as the mechanism's restriction to the disruption of the cell wall and plasm membrane and the emergence of resistance and toxicity, each candidate's potential was not compared to the three primary categories of existing medications in the present study [38]. Pepstatin, the current inhibitor associated with the crystal structure of the protein target, was utilized because none of the available medicines were clinically admissible [38].

C. zeylanicum chemicals were examined in silico using Lipinski's rule of five, followed by molecular docking investigations [40]. All of the chemicals collected for this investigation met Lipinski's rule of five, which are the binding energies obtained for each ligand, hydrogen bond contacts, and other interaction [2,40]. The Hexadecenoic Acid compound possesses the maximum binding energy with the active site area of SAP 4, as seen in Fig. 1. Ou et al. investigated the inhibitory effect of Hexadecenoic Acid on biofilm formation and hyphae development in *C. albicans* (2022) [41]. This compound was shown to have fungicidal activity against *C. albicans* [42]. The binding efficiency of Hexadecenoic Acid with the active site of the SAP 5 protein was found to be high, while Hexadecenoic Acid has two hydrogen bonds at residue no. 85 and 86 with hydrophobic bonds help at residue no. 30 and 123 and some van der Waals interactions (Fig. 2), and this compound exhibited fungicidal activity against *C. albicans* [41,42]. In contrast, Pyrantel Hydrochloride compound possesses the maximum binding energy at the active site of the SAP 6. Pyrantel Hydrochloride is an antifungal to inhibit *C. albicans* biofilm [43]. On the basis of the investigated molecular interactions, a lead for the development of a medication that inhibits the SAP protein pathway of *C. albicans* was identified.

The molecular docking results show that SAP 4 and SAP 5 are the best target candidates with several interactions in their catalytic residues. Among several compounds from *C. zeylanicum*, there is Hexadecenoic Acid. Continued the interaction Hexadecenoic Acid with SAP 4 and SAP 5 to the molecular dynamics stage to compare its interaction and stability with Pepstatin. This study provides preliminary information regarding the protein SAP5's most potent inhibitor. Consequently, the proposed chemical can be employed as a guide to developing a lead compound for candidiasis medication discovery in future research. These residues may hold the key to the future discovery of a novel medicine or the development of existing ones via chemical structural change. Docking studies are a handy tool for predicting the interaction between a ligand and a receptor, yet, the method's simplification has limitations. Therefore, we can refine the docking data by employing molecular dynamic modeling to get more precise binding predictions.

5. Conclusion

C. zeylanicum extract compounds have potential as anti-candidiasis by inhibiting the enzyme SAP 4–6. Among the compounds analyzed, Cinnamaldehyde, Hexadecenoic Acid, and Pyrantel Hydrochloride had the lowest bond energies with the highest number of interactions with the catalytic site residues. It is the best candidate to inhibit the activity of the SAP 4–6 enzyme. However, Pyrantel Hydrochloride has a weaker interaction with SAP 6 based on the chemical bonds formed. Molecular dynamics simulations showed that Hexadecenoic Acid had a high potential to inhibit the growth of *C. albicans* by inhibiting SAP 4 and SAP 5.

ORCID iD authorship contribution statement

Vita Meylani: Conceptualization, Methodology, Writing – original draft. Rinaldi Rizal Putra: Data curation, Writing – original draft. Muhammad Miftahussurur: Writing – review & editing. Sukardiman Sukardiman: Supervision, Writing – review & editing. Feri Eko Hermanto: Software, Validation. Abdullah Abdullah: Visualization, Software.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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