

Selected Polyphenols from Date (*Phoenix dactylifera*) as Anti-Virulence of *Candida albicans* Through Multiple Enzyme Targets

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Abstract: *Candida albicans* (*C. albicans*) have long been attributed to various diseases like candidiasis and systemic diseases and exacerbate the symptoms of immunocompromised patients. *C. albicans* has enzymes that could function as drug targets to decrease its pathogenicity and eradicate the fungi. This research aimed to investigate the potency of selected polyphenols contained in dates (*Phoenix dactylifera*) in inhibiting important enzymes of *C. albicans* through molecular docking simulation. The structures of four target enzymes (Sap 1, Sap 2, Sap 3, Sap 5) of *C. albicans* and six selected polyphenol compounds from dates were downloaded from PDB and prepared using YASARA Structure. A molecular docking simulation was conducted using YASARA Structure. Docking results showed that procyanidin has a high binding affinity with target protein Sap 1 and Sap 5, while beta carotene has a high binding affinity with Sap 2 and Sap 3. The binding affinity range of all ligand-receptor complexes was as follows: Sap 1 (5.782 – 9.907 kcal/mol), Sap 2 (5.943 – 9.343 kcal/mol), Sap 3 (5.732 – 8.905 kcal/mol), and Sap 5 (5.873 – 9.430 kcal/mol). The interactions formed included hydrogen bonding, electrostatic and hydrophobic interactions, and unfavorable bindings. The data generated from molecular docking analysis warrant further experiments are necessary.

Keywords: *Candida albicans*; molecular docking; *Phoenix dactylifera*; polyphenols; Sap protein.

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1. Introduction

Candida albicans (*C. albicans*) is a dimorphic yeast and one of the most commonly known fungal members of the human microbiota. It has been reported to frequently cause mucosal and systemic infections [1,2]. *C. albicans* is also a commensal organism and part of the normal human microflora, with an estimated population of 50% [3,4]. Commonly, *C. albicans* can be found to colonize and grow in the mucous membranes of the mouth, tongue, gastrointestinal tract, vagina, and urinary tract [2,4–7]. Although yeast is usually harmless in individuals with a healthy immune system, the change of yeast into pathogens in an unhealthy immune system can be life-threatening, especially in hospitalized patients who are immunocompromised by pathogens (e.g., Human Immunodeficiency Virus) [3,8]. Extracellular hydrolytic enzymes are important as virulence factors in bacteria, protozoa, and yeasts. In the case of *C. albicans*, hydrolytic enzymes facilitate pathogenic and commensal

characteristics that can cause damage to host cell membranes, resulting in the invasion of mucosal surfaces and penetration of blood vessels. These enzymes can also evade host immune responses [9]. In *Candida* species, the role of secreted aspartic proteinase (Sap) enzyme has been proven experimentally. Sap has 10 gene families, namely Sap 1 to Sap 10, all of which play a role in the pathogenicity of *C. albicans*. Sap 1-Sap 3 aids in adhesion, phenotype switching, and mucosal infection, whereas Sap 5 causes systemic infection and aids biofilm formation [10,11]. Therefore, the Sap enzyme of *C. albicans* is a widely known target, and its inhibition is a promising strategy for developing anti-virulence drugs against *C. albicans* [10].

The ideal antifungal drug should exhibit no toxicity to human cells. The search for a new drug candidate originating from plants is known to take a long time and require high cost. In recent years, *in silico* methods have been developed for rapid drug design, optimizing time, saving costs, and increasing the success rate. One of the most commonly used *in silico* methods is molecular docking. Molecular docking is a computational simulation that predicts interactions between two structures, such as a protein and a ligand, or between two interacting proteins. The simulation result includes observed interactions that could be analyzed, such as electrostatic, van der Waals, coulombic interactions, and hydrogen bonding. In addition to the resulting types of interactions, bond energy indicates the potential of bond formation between two complex structures [12–14].

Date (*Phoenix dactylifera*) is known as the most prominent energy source for people in the Arabian peninsula. The basis for studying the medicinal properties of dates comes from the prophetic tradition in Islam, especially from Prophet Mohammed, who proposed using dates as spices and medicinal plants to cure various diseases. Medical literature in Islamic history also shows various advantages of dates as traditional medicine. The therapeutic effect of dates is largely attributed to their polyphenol content. Polyphenols from plants are natural compounds found in vegetables, fruit, and some products, such as juices and oils derived from fruit and vegetables. Generally, the chemical structure of polyphenols is divided into several categories; phenolic acids, flavonoids, stilbene, and many other derivatives [15–17]. The structural formulas of several kinds of polyphenols found in dates have been reviewed and are used in this study [15]. The dates' fruits, leaves, and seeds are known to have antimicrobial and antifungal activities, including the yeast *C. albicans* [16]. In the present study, molecular docking analysis was carried out using polyphenols originating from dates toward various target enzymes in *C. albicans* to analyze the molecular interactions formed in search of potential enzyme inhibitors.

2. Materials and Methods

2.1. Protein structure preparation.

The three-dimensional protein structures from *C. albicans* Sap 1 (PDB ID: 2QZW), Sap 2 (PDB ID 1EAG), Sap 3 (PDB ID: 2H6T), and Sap 5 (PDB ID: 2QZX) were obtained from the Protein Data Bank (PDB) (<https://www.rcsb.org/>). Preparation of protein structures to be used as receptors was carried out using YASARA (Yet Another Artificial Reality Application) Structure (Bioinformatics 30,2981-2982 Version 19.9.17). Every protein was prepared by removing water molecules and unnecessary chains, adding hydrogen atoms, and removing the native ligand [18–21]. The energy of all protein targets was minimized [21,22]. This study used chain A for molecular docking [23].

2.2. Ligand structure preparation.

Three-dimensional structures of ligands used were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), beta carotene (PubChem CID: 5280489), ferulic acid (PubChem CID: 445858), lutein (PubChem CID: 5281243), procyanidin (PubChem CID: 107876), quercetin (5280343), syringic acid (10742). The 3D structures were prepared using YASARA Structure to add hydrogen atoms and to minimize the energy on the ligand structure, according to YASARA manuals [20–24].

2.3. Molecular docking.

YASARA Structure, an AutoDock-based software, was used to carry out molecular docking to determine the dissociation constant (Kd) and the binding energy from the protein-ligand complex from the docking process [25–27]. Ligand docking to several target receptors of *C. albicans* was carried out by choosing the AutoDock Vina method within the dock_run file (runs: 25, Amber 03, set size automatically, extend 10 Å, shape cube (around selected atoms) [21,28–31]. Other parameters were set as default [30]. In the docking method, the receptor was set to be rigid, and the ligands were in flexible conformations [12,32].

2.4. Data analysis and docking result visualization.

BIOVIA Discovery Studio Visualizer v21.1.0.20298 software was employed to obtain data and visualize molecular docking results by using the 'ligand interactions' menu to analyze types of interactions formed between receptor-ligand and the corresponding amino acid residues. Visualization was carried out to obtain images of receptor-ligand's 2D and 3D structure [28,33].

3. Results and Discussion

This research used YASARA Structure software for molecular docking analysis of selected polyphenol compounds from date (*Phoenix dactylifera*) to inhibit Sap 1 – Sap 3 and Sap 5 of *Candida albicans*. Docking results include binding energy (kcal/mol), dissociation constant, and contacting receptor residues. The molecular docking analysis was based on several parameters in molecular interactions, namely dissociation constant (Kd), binding energy, and interactions formed by Pandey [33]. BIOVIA Discovery Studio software was used to visualize the molecular interactions.

Failure to design drug candidates to be marketed could be caused by several factors, like inaccuracy in choosing drug targets in pre-clinical research. The bioinformatics approach could provide a cheaper, faster, and more accurate result to identify potential drug candidates for certain protein targets [34,35]. This research employed the molecular docking analysis method, an *in silico*-based approach.

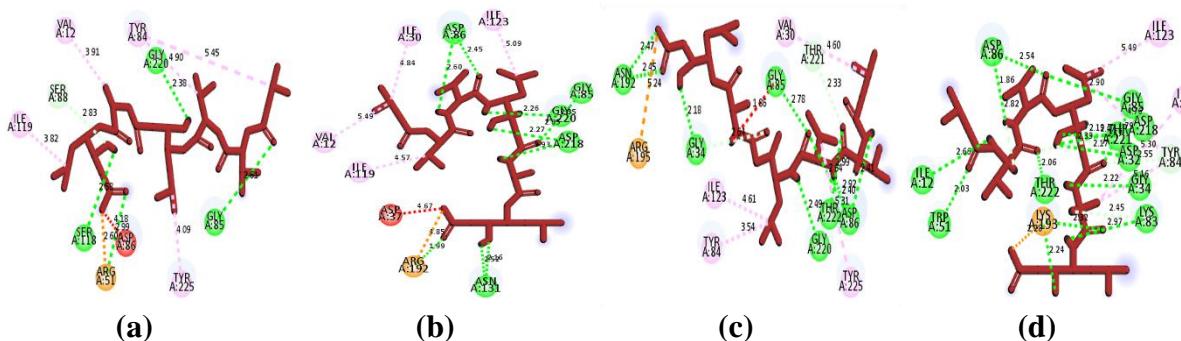
3.1. Method validation and molecular docking.

The redocking procedure was carried out with a crystallized inhibitor in complex with the receptor. Receptors with bound crystallized inhibitors can be obtained from RCSB PDB. The receptor-inhibitor pairs were Sap 2 with A70450, Sap 3 with pepstatin, and Sap 5 with pepstatin. All target receptors were redocked with A7450 and pepstatin as standards or comparative inhibitors in analyzing docking scores and interactions formed between receptors

and test ligands [36]. Sap 1 is reported to be free of the complex inhibitor [10], therefore, pepstatin was obtained from another Sap protein (Sap 3 and Sap 5) for redocking. Redocking results are shown in Table 1, and the dissociation constant is shown in Table 2. Figure 1 is the visualization of docking results to demonstrate the existing interactions of standard inhibitors of Sap.

Table 1. Redocking results of standard inhibitors.

Enzyme	Standard inhibitor	
	Pepstatin A	A70450
Sap 1	A VAL 12 A SER 13 A ILE 30 A ASP 32 A GLY 34 A SER 35 A ARG 51 A ILE 82 A GLY 83 A TYR 84 A GLY 85 A ASP 86 A SER 88 A SER 118 A ILE 119 A PRO 120 A ILE 123 A ASN 131 A ARG 192 A GLU 193 A ARG 195 A LEU 216 A ASP 218 A GLY 220 A THR 221 A THR 222 A ILE 223 A TYR 225 A ALA 303 A ILE 305	A VAL 12 A SER 13 A ILE 30 A ASP 32 A GLY 34 A SER 35 A LYS 49 A ARG 51 A ILE 82 A GLY 83 A TYR 84 A GLY 85 A ASP 86 A SER 88 A SER 118 A ILE 119 A PRO 120 A ASN 131 A ARG 192 A GLU 193 A ARG 195 A LEU 216 A ASP 218 A GLY 220 A THR 221 A THR 222 A ILE 223 A TYR 225 A ALA 303 A ILE 305
Sap 2	A GLU 10 A VAL 12 A THR 13 A ILE 30 A ASP 32 A GLY 34 A SER 35 A ILE 82 A GLY 83 A TYR 84 A GLY 85 A ASP 86 A SER 88 A SER 118 A ILE 119 A ASP 120 A GLN 121 A ILE 123 A ASN 131 A ALA 133 A ARG 192 A GLU 193 A LEU 216 A ASP 218 A GLY 220 A THR 221 A TYR 225 A ALA 303 A ILE 305	A VAL 12 A THR 13 A ILE 30 A GLY 34 A SER 35 A THR 50 A TYR 51 A ILE 82 A GLY 83 A TYR 84 A GLY 85 A ASP 86 A SER 88 A SER 118 A ILE 119 A ASP 120 A ILE 123 A ASN 131 A ALA 133 A ARG 192 A LEU 216 A ASP 218 A GLY 220 A THR 221 A THR 222 A TYR 225 A ASN 301 A ALA 303 A ILE 305
Sap 3	A VAL 12 A SER 13 A VAL 30 A ASP 32 A GLY 34 A SER 35 A ILE 82 A GLU 83 A TYR 84 A GLY 85 A ASP 86 A THR 88 A VAL 119 A ILE 123 A ASN 192 A GLU 193 A LEU 216 A ASP 218 A GLY 220 A THR 221 A THR 222 A TYR 225 A ILE 305	A GLU 10 A VAL 12 A SER 13 A VAL 30 A ASP 32 A GLY 34 A SER 35 A TYR 84 A GLY 85 A ASP 86 A THR 88 A VAL 119 A ASP 120 A GLN 121 A ILE 123 A ASP 218 A GLY 220 A THR 221 A THR 222 A ILE 223 A TYR 225 A GLN 295 A LEU 297 A SER 301 A ILE 305
Sap 5	A ILE 12 A THR 13 A ILE 30 A ASP 32 A THR 33 A GLY 34 A SER 35 A TRP 51 A ILE 82 A LYS 83 A TYR 84 A GLY 85 A ASP 86 A SER 88 A ALA 119 A ARG 120 A ILE 123 A ALA 133 A LYS 193 A LEU 216 A ASP 218 A GLY 220 A THR 221 A THR 222 A ILE 223 A TYR 225 A ARG 297 A ARG 299 A ILE 305	A ALA 11 A ILE 12 A THR 13 A ILE 30 A ASP 32 A TRP 51 A TYR 84 A GLY 85 A ASP 86 A SER 88 A ALA 119 A ARG 120 A ILE 123 A GLY 220 A THR 221 A THR 222 A ILE 223 A TYR 225 A ASP 245 A LYS 250 A VAL 251 A TYR 252 A PHE 281 A GLU 295 A VAL 296 A ARG 297 A ILE 298 A ARG 299 A GLU 300 A ILE 305



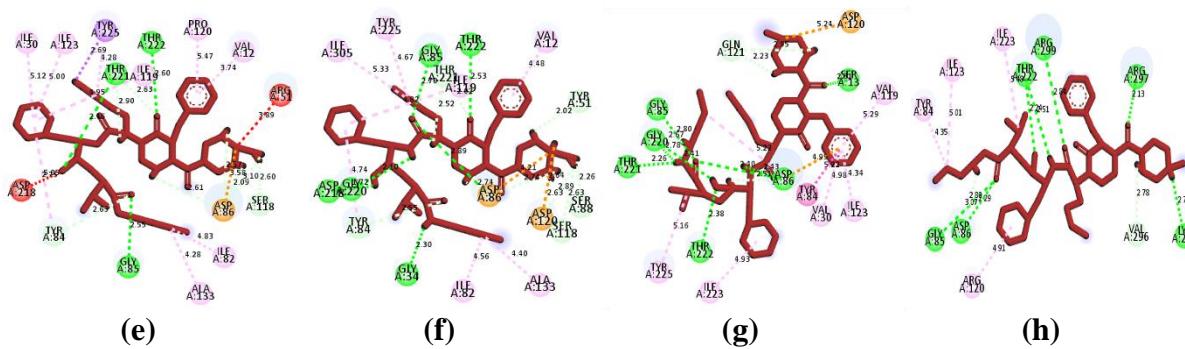


Figure 1. Visualization of standard inhibitors: (a) Pepstatin with Sap 1; (b) Pepstatin with Sap 2; (c) Pepstatin with Sap 3; (d) Pepstatin with Sap 5; (e) A70450 with Sap 1; (f) A70450 with Sap 2; (g) A70450 with Sap 3; (h) A70450 with Sap 5.

There were six selected polyphenols from dates used in the molecular docking procedure, ferulic acid, syringic acid, quercetin, procyanidin, beta carotene, and lutein. The receptors used in this research were Sap 1, Sap 2, Sap 3, and Sap 5. First molecular docking was carried out with Sap 1 as a receptor, using pepstatin and A70450 as standard inhibitors. Pepstatin had binding energy of 7.432 kcal/mol; this value was lower than that of A70450, which was 9.613 kcal/mol. However, both still have lower binding energy values than the test ligands. Procyanidin was the test ligand that exhibited the highest binding energy with Sap 1, with a 9.907 kcal/mol value. In interaction with Sap 1, the binding energy for the test ligands beta carotene, lutein, quercetin, ferulic acid, and syringic acid were 8.653 kcal/mol, 8.189 kcal/mol, 7.831 kcal/mol, 6.065 kcal/mol, and 5.783 kcal/mol, respectively. Hence, procyanidin had the highest binding energy with Sap 1 compared to the standard inhibitors.

The second docking was carried out with Sap 2 receptor. Two standard inhibitors, pepstatin and A70450, showed binding energy of 7.830 kcal/mol and 8.970 kcal/mol, respectively. Those values were still lower than the binding energy of the test ligands. The highest binding energy on Sap 2 was observed from beta carotene with the value of 9.343 kcal/mol; however, lutein also had binding energy of 9.333 kcal/mol; thus, both ligands had a binding energy value of more than 9 kcal/mol with only 0.010 kcal/mol difference. In interaction with Sap 2, the binding energy for test ligands procyanidin, quercetin, ferulic acid, and syringic acid were 8.074 kcal/mol, 7.413 kcal/mol, 6.580 kcal/mol, and 5.943 kcal/mol, respectively. Syringic acid showed the lowest binding energy with Sap 2 compared to all standard and test ligands.

The third docking was conducted with Sap 3 receptor. Pepstatin and A70450 as standard inhibitors showed binding energy of 8.000 kcal/mol and 8.558 kcal/mol, respectively. There were two test ligands with higher binding energy compared to the standard inhibitors: beta carotene (8.905 kcal/mol) and lutein (8.865 kcal/mol). In interaction with Sap 3, the binding energy for test ligands procyanidin, quercetin, syringic acid, and ferulic acid were 8.414 kcal/mol, 8.073 kcal/mol, 5.732 kcal/mol, and 6.589 kcal/mol, respectively.

The final docking was performed with Sap 5 receptor. The standard inhibitors, pepstatin and A70450, showed binding energy of 8.442 kcal/mol and 9.238 kcal/mol, respectively. Procyanidin was the only test ligand with binding energy higher than the standard inhibitors, which was 9.430 kcal/mol. In interaction with Sap 5, the binding energy for test ligands lutein, beta carotene, quercetin, ferulic acid, and syringic acid were 8.569 kcal/mol, 8.524 kcal/mol, 8.166 kcal/mol, 7.069 kcal/mol, and 5.873 kcal/mol, respectively. Compounds showing more positive binding energy tend to interact better with receptors [28]. In this research, it is observed that I) standard inhibitors exhibit lower binding energies compared to test ligands, II) the test

ligands beta carotene, lutein, and procyanidin is the most dominant test ligands with higher binding energy value with target receptors according to docking results, and III) ferulic acid and syringic acid are the most dominant ligands showing lower binding energy values. All docking scores of test ligands and Sap 1, Sap 2, Sap 3, and Sap 5 are shown in Figure 2. Dissociation constant values are provided in Table 2.

The molecular docking method could show potential compounds as drug candidates according to their ability to form interactions with certain protein targets [36–41]. Also, molecular docking is one of the most important tools in structure-based drug design [42,43]. According to the molecular docking simulation results, the test ligands used in this research are known to have higher binding energies than standard inhibitors.

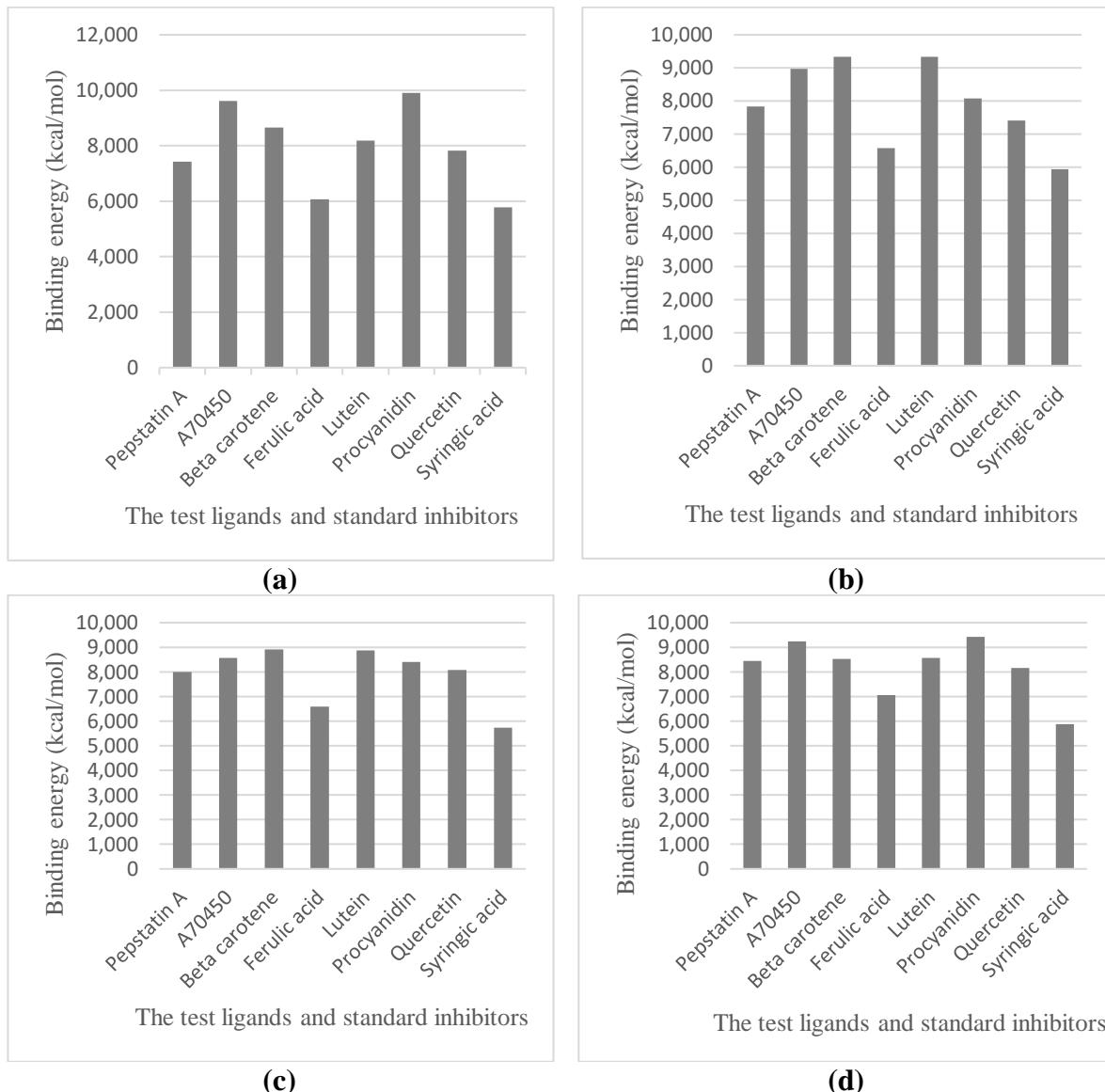


Figure 2. Molecular docking result of test ligands and four target receptors: **(a)** standard inhibitors and test ligands with Sap 1; **(b)** standard inhibitors and test ligands with Sap 2; **(c)** standard inhibitors and test ligands with Sap 3; **(d)** standard inhibitors and test ligands with Sap 5.

Table 2. Dissociation constant of test ligands and target receptors.

Compound name	Dissociation constant (pM)			
	Sap 1	Sap 2	Sap 3	Sap 5
Pepstatin	3566742.5	1821939.25	1367484	648532.812
A70450	89862.304	266012.968	533215.562	169221.765
Beta carotene	454220.687	141739.265	296857.781	564709.562
Ferulic acid	35834064	15024362	14797862	6581945.5

Compound name	Dissociation constant (pM)			
	Sap 1	Sap 2	Sap 3	Sap 5
Lutein	993993.187	144151.875	317591.468	523407.218
Procyanidin	54710.753	1206922.875	679917.5	122382.226
Quercetin	1818866.75	3682976.5	1208961.625	1033338.562
Syringic acid	57677284	44027420	62862012	49548888

3.2. Analysis and visualization of molecular docking results.

Some of the polyphenols found in dates belong to phenolic acids (syringic acid and ferulic acid), flavonoids (quercetin and procyanidin), and carotenoids (beta carotene and lutein) compound groups [15]. Shown in Table 3 is the summary of the interactions between test ligands and Sap 1, Sap 2, Sap 3, and Sap 5. It has been observed that all four receptors have the same catalytic residues, which are located on Asp32 and Asp218 [44]. Sap 1 and beta carotene interact with hydrophobic interactions, while ferulic acid, lutein, quercetin, and syringic acid show hydrophobic and hydrogen bonding. The hydrogen bondings formed between test ligands and Sap 1 are attributed to the presence of the hydroxyl group OH. There are two ligands that interact with the catalytic residues of Sap – ferulic acid with A:UNK1:H as H-Donor and A:ASP32:OD1 as H-Acceptor, and syringic acid with A:UNK1:H as H-Donor and A:ASP218:OD1 as H-Acceptor.

The interaction between test ligands and Sap 2 shows various interactions. Lutein has hydrogen bonding in the OH group, ferulic acid, procyanidin, quercetin, and syringic acid. Only beta-carotene shows all-hydrophobic interactions. Quercetin forms hydrogen bonding on the catalytic site of Sap 2, with A:UNK1:H as H-Donor and A:ASP32:OD1 as H-Acceptor. Interactions between test ligands and Sap 3 that form hydrogen bonding and hydrophobic interactions are those of procyanidin, ferulic acid, quercetin, and syringic acid. Quercetin interacts with the catalytic residue of Sap 3 through hydrogen bonding with A:UNK1:H as H-Donor and A:ASP218:OD2 as H-Acceptor. There are two test ligands that only form hydrophobic interactions.

Interactions between test ligands and Sap 5 that formed hydrogen bonding and hydrophobic interactions are of ferulic acid, procyanidin, quercetin, and syringic acid. Ferulic acid formed hydrogen bonding with the catalytic residue A:ASP218:OD2 as H-Acceptor and A:UNK1:H as H-Donor. It has been known that the presence of hydrogen bonding is one of the most important factors in increasing the binding affinity of ligand and protein receptors [42].

Hydrogen bonding is important in determining the specificity of ligand binding [45–47], and its significance for biomacromolecules' properties and structures has been defined theoretically and experimentally [45]. The literature states that a strong hydrogen bonding is less than 2.3 Å in the distance. Strong hydrogen bonding is the most significant factor contributing to the increased binding affinity between receptor and drug candidates [47–51]. The role of hydrogen bonding in binding affinity has been elaborated extensively. Despite its importance, hydrogen bonding is not the only interaction acquiring a crucial role in ligand-receptor interaction. Hydrophobic interaction is also observed to play a significant role in ligand-receptor binding. The average amount of hydrophobic atoms in commercial drugs is 16, with one to two donors and three to four acceptors. It shows the importance of hydrophobic interactions in *in silico* drug design. The interactions can increase the binding affinity of the interface of the drug target [35,52,53].

In this research, we found several electrostatic interactions formed between ligand and receptor; Sap 2 with procyanidin and quercetin, Sap 3 with ferulic acid, and Sap 5 with

procyanidin. The electrostatic interactions formed between those receptor-ligands are all of the same type: Pi-Anion. Electrostatic interactions have been observed to increase the stability of the ligand-receptor complex [54]. It has also been found that the interaction determines the maximum efficiency of ligand binding [55,56].

Unfavorable binding can affect the stability of drug activity. The formation of any unfavorable binding within the ligand-receptor complex is known to decrease its stability due to the strength of the repulsion between two molecules and atoms [57]. According to the explanation, unfavorable binding is responsible for the decreased stability of receptor-ligand complex between Sap 1-procyanidin with unfavorable donor-donor, Sap 2-procyanidin with unfavorable donor-donor, Sap 3-procyanidin with two unfavorable donor-donor, Sap 3-ferulic acid with unfavorable acceptor-acceptor, Sap 5-ferulic acid with two unfavorable donor-donor, and Sap 5-syringic acid with two unfavorable acceptor-acceptor.

The binding of the ligand to the protein target's active site indicates the ligand's probability of delivering functional modulations in target molecules. This idea is supported by other studies which have shown that ligands and their binding to the active site of proteins could cause functional alterations of the protein as the target molecule [33]. The compounds used in this research are known to be able to bind at the active site of the substrate binding pocket of each Sap protein [43]. In determining the active site of the substrate binding pocket of each Sap, we used the studies from Borelli *et al.* [44] and Borelli *et al.* [3]. The most crucial substrate binding pockets on Sap are S3 and S4 pockets [3,10]. Flavonoids from endophytic fungi (EF) extracts have also been studied as potential inhibitors of N-myristoyltransferase of *C. albicans* through molecular docking simulation. Flavonoid heterosides like quercetin from *Equisetum giganteum* extract have been proven to inhibit the formation of the oral biofilm of *Candida* [34,43,58].

Table 3. Analysis of interactions formed within the ligand-receptor complex from molecular docking result.

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
Sap 1	Beta carotene	A:ALA133 - A:UNK1	3,90093	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA133 - A:UNK1:C	4,25334	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA133 - A:UNK1:C	4,31533	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	4,42096	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	4,93537	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE82	4,67457	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE223	3,94045	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE223	4,54335	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU297	4,8391	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE223	4,66594	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE82	4,42287	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU216	5,27186	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR84 - A:UNK1:C	4,05291	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR84 - A:UNK1	5,25095	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR225 - A:UNK1:C	4,55038	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Ferulic acid	A:SER88:HG - A:UNK1:O	2,57707	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP32:OD1	2,35976	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:GLY220:C,O;THR221:N - A:UNK1	4,46099	Hydrophobic	Amide-Pi Stacked	Amide	Pi-Orbitals

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
Lutein	Lutein	A:UNK1:H - A:HIS11:O	2,69507	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:GLU132:O	2,91961	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ALA133 - A:UNK1	5,03533	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA133 - A:UNK1:C	3,65716	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA133 - A:UNK1:C	3,78157	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	4,64053	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE223	4,12319	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE82	4,38439	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE82	5,12165	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE223	4,63688	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU297	4,79964	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE223	4,71949	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	5,16815	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR84 - A:UNK1	5,02554	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR225 - A:UNK1:C	4,87329	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
Procyanidin	Procyanidin	A:GLY34:H - A:UNK1:O	2,78748	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:SER88:HG - A:UNK1:O	2,80879	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP86:OD1	2,78581	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP218:OD2	2,00002	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ALA303 - A:UNK1	5,44946	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ILE305 - A:UNK1	5,22345	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ALA303	3,80305	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:ASP86:H - A:UNK1:H	1,52369	Unfavorable	Unfavorable Donor-Donor	H-Donor	H-Donor
Quercetin	Quercetin	A:SER13:HG - A:UNK1:O	2,51866	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:SER118:HG - A:UNK1:O	2,70667	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:GLY220:O	1,76486	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:UNK1:O	1,89061	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP86:OD2	2,20435	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1 - A:ILE119	5,23094	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:ILE119	4,75688	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:PRO120	5,05339	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
Syringic acid	Syringic acid	A:GLY85:H - A:UNK1:O	2,33204	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ASP86:H - A:UNK1:O	2,40651	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:SER88:HG - A:UNK1:O	2,99131	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP218:OD1	3,02596	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
		A:GLY85:HA2 - A:UNK1:O	3,04774	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H2 - A:THR221:OG1	2,69289	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:C - A:ILE305	5,23925	Hydrophobic	Alkyl	Alkyl	H-Acceptor
		A:UNK1:C - A:ILE119	4,19866	Hydrophobic	Alkyl	Alkyl	H-Acceptor
Sap 2	Lutein	A:UNK1:H - A:PHE58:O	2,86971	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:PHE58:O	2,25019	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:ALA303 - A:UNK1:C	4,00953	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA303 - A:UNK1:C	4,18313	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU216	4,94081	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	4,83797	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LYS62	4,7204	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	5,10065	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE30	5,22905	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	4,92889	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE30	5,16701	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE30	4,98426	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE30	4,0473	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE123	3,91831	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR84 - A:UNK1	4,61999	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Beta carotene	A:LYS62 - A:UNK1	5,35725	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LYS62	4,72846	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU216	4,65709	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	4,32037	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	5,1755	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LYS62	5,33177	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	5,35698	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE30	4,94277	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE119	3,83004	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE30	5,08669	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE119	4,72859	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR84 - A:UNK1:C	4,84269	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR84 - A:UNK1:C	4,40282	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR84 - A:UNK1	4,52853	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Ferulic acid	A:THR221:HG1 - A:UNK1:O	2,89491	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:SER88:HB1 - A:UNK1:O	2,86806	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR84 - A:UNK1	4,2597	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
Procyanidin		A:THR222:H - A:UNK1:O	2,19519	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR225:HH - A:UNK1:O	2,22541	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP120:OD1	2,93652	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP120:OD1	2,9294	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:UNK1:O	2,0083	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
		A:UNK1:H - A:VAL12:O	2,16285	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP218:OD2	2,30745	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:THR222:OG1	1,97411	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:THR221:HA - A:UNK1:O	2,7949	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:GLY220:O	2,81719	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP86:OD2	3,00321	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:ASP120:OD1 - A:UNK1	3,92901	Electrostatic	Pi-Anion	Negative	Pi-Orbitals
		A:UNK1:H - A:TYR84	2,9764	Hydrogen Bond	Pi-Donor Hydrogen Bond	H-Donor	Pi-Orbitals
		A:TYR84 - A:UNK1	4,53666	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:UNK1 - A:UNK1	3,61293	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:THR222:H - A:UNK1:H	2,55679	Unfavorable	Unfavorable Donor-Donor	H-Donor	H-Donor
		A:GLY85:H - A:UNK1:O	2,89161	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ASP86:H - A:UNK1:O	2,46019	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP32:OD1	2,39317	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP120:OD1	2,13167	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:GLY34:HA2 - A:UNK1:O	2,50638	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ASP218:OD2 - A:UNK1	3,9887	Electrostatic	Pi-Anion	Negative	Pi-Orbitals
	Syringic acid	A:UNK1 - A:ILE119	5,33855	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1:H - A:ASP32:OD1	2,18438	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:GLY85:HA2 - A:UNK1:O	2,65574	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR84 - A:UNK1	4,76155	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:UNK1:C - A:ILE119	4,25948	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	5,25143	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR84 - A:UNK1:C	4,61308	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Procyanidin	A:UNK1:H - A:ASP37:OD2	2,57354	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:GLU132:OE2	2,64932	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:GLU132:OE2	2,38059	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:UNK1:O	2,38331	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
		A:UNK1:H - A:SER81:O	2,77988	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:SER36:HB1 - A:UNK1:O	2,51776	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:GLU193:HA - A:UNK1:O	2,54996	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP37:OD2	3,02121	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:GLU83:H - A:UNK1	3,21974	Hydrogen Bond	Pi-Donor Hydrogen Bond	H-Donor	Pi-Orbitals
		A:ASN192:HD22 - A:UNK1	3,1898	Hydrogen Bond	Pi-Donor Hydrogen Bond	H-Donor	Pi-Orbitals
		A:UNK1 - A:UNK1	4,20322	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:ILE82 - A:UNK1	5,05497	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE82	5,17175	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:SER36:HG - A:UNK1:H	2,44934	Unfavorable	Unfavorable Donor-Donor	H-Donor	H-Donor
		A:LYS129:HZ3 - A:UNK1:H	1,56277	Unfavorable	Unfavorable Donor-Donor	H-Donor	H-Donor
		A:SER35:HB2 - A:UNK1:O	2,5194	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H2 - A:GLY220:O	2,87954	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:ASP86:OD2 - A:UNK1	4,84813	Electrostatic	Pi-Anion	Negative	Pi-Orbitals
		A:TYR84 - A:UNK1	5,01373	Hydrophobic	Pi-Pi T-shaped	Pi-Orbitals	Pi-Orbitals
	Ferulic acid	A:UNK1:C - A:VAL12	5,0726	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:VAL30	5,2009	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:VAL119	5,31251	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:ILE123	4,38464	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:ASP218:OD2 - A:UNK1:O	2,84559	Unfavorable	Unfavorable Acceptor-Acceptor	H-Acceptor	H-Acceptor
		A:UNK1:H - A:ASP86:OD2	2,78595	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP218:OD2	2,63762	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:GLY34:HA2 - A:UNK1:O	2,90221	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR84 - A:UNK1	4,42393	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:UNK1 - A:VAL30	5,41373	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:VAL119	5,22699	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Quercetin	A:UNK1 - A:ILE123	5,35332	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:VAL30	4,78487	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:VAL119	5,36592	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:ILE123	5,18843	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:VAL30 - A:UNK1	4,42171	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:VAL119 - A:UNK1	4,96165	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU216	4,85922	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	5,1869	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE123	5,30498	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE123	3,69071	Hydrophobic	Alkyl	Alkyl	Alkyl
	Lutein	A:UNK1:C - A:VAL119	4,89513	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR84 - A:UNK1	4,67616	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR84 - A:UNK1:C	4,21528	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1	4,61575	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1:C	4,74491	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
Sap 5	Beta-carotene	A:TYR303 - A:UNK1:C	3,53288	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:ALA281 - A:UNK1	4,26409	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA281 - A:UNK1	4,1611	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA281 - A:UNK1:C	3,74908	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:PRO282 - A:UNK1	5,36124	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU216	5,33444	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU216	4,97426	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	4,37838	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE305	5,15985	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE305	5,34495	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL12	5,30856	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LEU297	4,42808	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE223	5,18164	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:LEU297	4,61534	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE223	4,36005	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1 - A:ILE223	4,11713	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR225 - A:UNK1:C	4,28405	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR225 - A:UNK1	4,75421	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1	4,45543	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1:C	4,96414	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1	5,04274	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1:C	3,96758	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR303 - A:UNK1:C	5,22682	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Syringic acid	A:UNK1:H3 - A:GLY34:O	2,94952	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H3 - A:THR221:OG1	2,7204	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR84 - A:UNK1	4,4106	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:TYR84 - A:UNK1:C	4,86975	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
Sap 5	Ferulic acid	A:GLY85:H - A:UNK1:O	2,73799	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG120:HH12 - A:UNK1:O	2,35697	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:ASP218:OD2	2,07118	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ALA119:HA - A:UNK1:O	2,62666	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H3 - A:THR221:OG1	2,76774	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR84 - A:UNK1	4,84338	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:ARG120:H - A:UNK1:H	1,54487	Unfavorable	Unfavorable Donor-Donor	H-Donor	H-Donor
		A:THR221:HG1 - A:UNK1:H	1,77429	Unfavorable	Unfavorable Donor-Donor	H-Donor	H-Donor
	Beta carotene	A:VAL251 - A:UNK1	4,7336	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE123	4,98109	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE30	3,86043	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE123	4,99251	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LYS243	4,34537	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ARG120	4,73214	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:LYS243	3,82409	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL251	3,69513	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL251	4,40847	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TRP51 - A:UNK1:C	4,87514	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TRP51 - A:UNK1	4,50188	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TRP51 - A:UNK1:C	4,2419	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TRP51 - A:UNK1	4,83717	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TRP51 - A:UNK1:C	5,24868	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
Lutein		A:TYR84 - A:UNK1	5,0349	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:TYR84 - A:UNK1:C	3,79907	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:PHE291 - A:UNK1	4,88697	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:PHE291 - A:UNK1:C	4,92554	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:PHE291 - A:UNK1:C	4,93001	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:ALA11 - A:UNK1	3,38399	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA11 - A:UNK1:C	4,23455	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ALA11 - A:UNK1	4,87453	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ARG297 - A:UNK1	4,34233	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ARG299 - A:UNK1	4,68471	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ARG299 - A:UNK1	5,15255	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL251	4,79515	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ARG299	4,78381	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ARG299	4,08569	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:VAL251	4,04725	Hydrophobic	Alkyl	Alkyl	Alkyl
	Procyanidin	A:UNK1 - A:ILE223	5,37393	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:TYR252 - A:UNK1:C	5,27834	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:PHE281 - A:UNK1:C	5,2301	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:PHE281 - A:UNK1	4,73411	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:PHE281 - A:UNK1:C	5,21335	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:ARG52:H - A:UNK1:O	2,35715	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG297:HE - A:UNK1:O	2,60645	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG297:HH11 - A:UNK1:O	2,68841	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG299:HE - A:UNK1:O	1,89261	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG299:HH21 - A:UNK1:O	2,29072	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
Quercetin		A:UNK1:H - A:VAL296:O	2,4611	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:VAL296:O	2,10694	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:H - A:GLU295:OE1	2,42875	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		A:TRP51:HA - A:UNK1:O	2,82748	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG297:HA - A:UNK1:O	2,07456	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:ARG297:NH1 - A:UNK1	4,96529	Electrostatic	Pi-Cation	Positive	Pi-Orbitals
		A:TRP51 - A:UNK1	4,19906	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:TRP51 - A:UNK1	4,11113	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:UNK1 - A:UNK1	5,56415	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:UNK1 - A:VAL251	4,45308	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
Syringic acid		A:UNK1 - A:VAL251	4,51943	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:UNK1 - A:ARG299	4,41209	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		A:GLY34:HA2 - A:UNK1:O	2,87011	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:TYR84 - A:UNK1	5,37421	Hydrophobic	Pi-Pi Stacked	Pi-Orbitals	Pi-Orbitals
		A:UNK1 - A:ALA119	4,96734	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
	Syringic acid	A:ASP86:H - A:UNK1:O	2,41906	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor

Protein	Ligand	Name	Distance (Å)	Category	Types	From chemistry	To chemistry
		A:GLY34:HA2 - A:UNK1:O	2,51411	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
		A:UNK1:C - A:ILE30	4,41761	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:UNK1:C - A:ILE123	4,10176	Hydrophobic	Alkyl	Alkyl	Alkyl
		A:ASP32:OD2 - A:UNK1:O	2,82317	Unfavorable	Unfavorable Acceptor-Acceptor	H-Acceptor	H-Acceptor
		A:ASP86:OD1 - A:UNK1:O	2,93948	Unfavorable	Unfavorable Acceptor-Acceptor	H-Acceptor	H-Acceptor

We visualize the molecular docking result from the YASARA structure using BIOVIA Discovery Studio. Visualization showed residues that contributed to ligand-receptor binding, types of bonds, and formed interactions [33]. The result of this research showed that the test ligands that have the best binding affinity with target receptors are procyanidin with Sap 1 (Figure 3a), beta carotene with Sap 2 (Figure 3b), beta carotene with Sap 3 (Figure 3c), and procyanidin with Sap 5 (Figure 3d). The structures of the complex are used for interactive visualization [28].

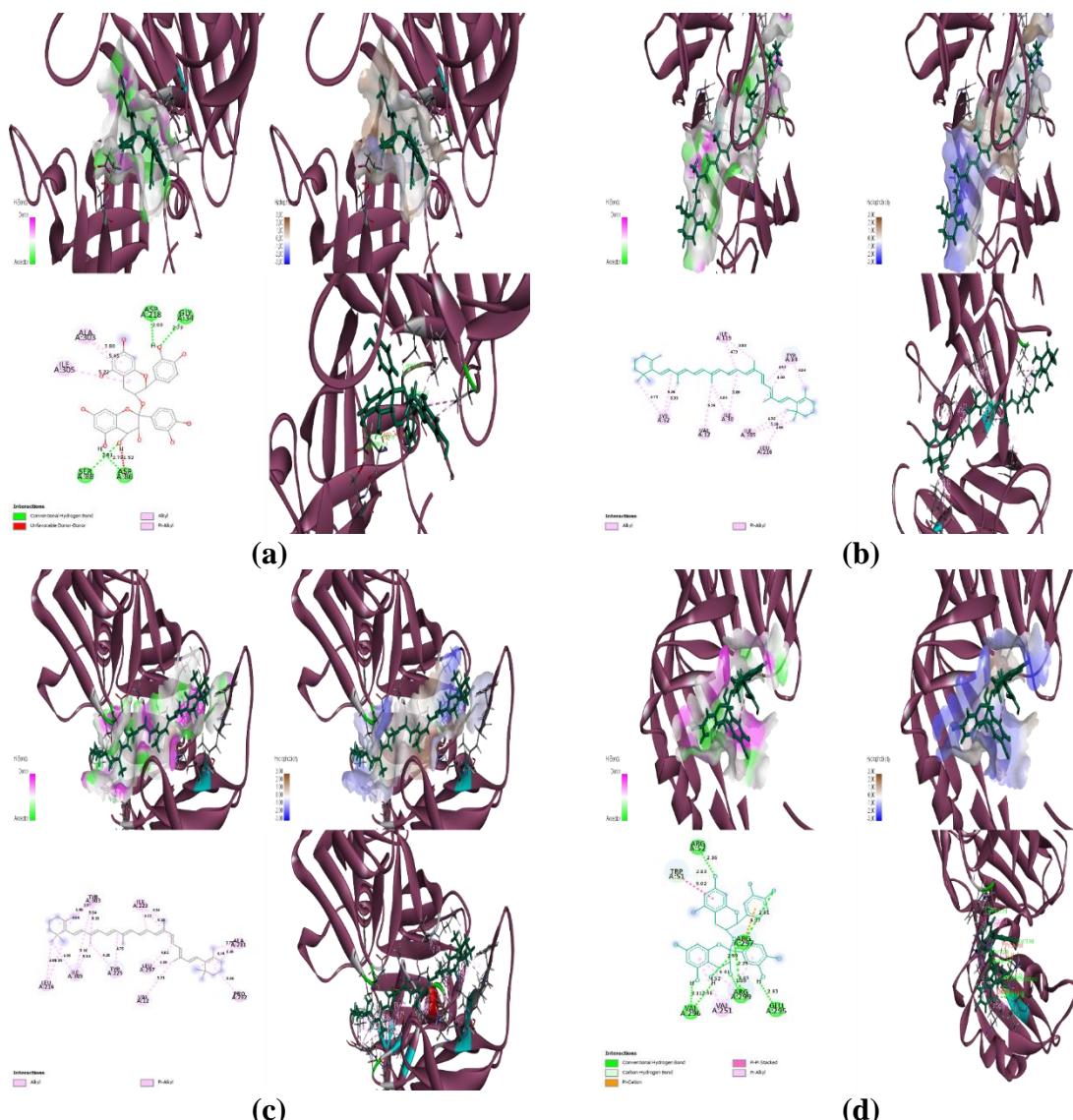


Figure 3. Visualization from the best docking results: (a) 2D and 3D interactions of Procyanidin with Sap 1; (b) 2D and 3D interactions of Beta carotene with Sap 2; (c) 2D and 3D interactions of beta carotene with Sap 3; and (d) procyanidin with Sap 5.

4. Conclusions

Using molecular docking simulation, we found selected polyphenols from dates to be potential inhibitors of four target enzymes of *C. albicans* (Sap 1, 2, 3, and 5), which could decrease its pathogenicity. According to binding affinity analysis, each target enzyme has a potential ligand as the best drug candidate; Sap 1 with Procyanidin, Sap 2 with Beta carotene, Sap 3 with Beta carotene, and Sap 5 with Procyanidin. We also analyzed the bonds and interactions formed within the ligand-receptor complexes. The presence of favorable interactions between ligands and important amino acid residues on each receptor makes our research an important starting point for upcoming studies in finding the best inhibitors for important enzymes of *C. albicans*.

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Conflicts of Interest

The authors declare no conflict of interest.

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