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Expansion of the antifungal activities through in silico docking study of compounds from Albizia lebbeck fruits

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Abstract

The development of new computational and experimental techniques that are efficient, fast, and accurate has become a priority for researchers in all domains around the world. The present manuscript deals with the computational investigation of quercitrin (**1**), lebbeckisoetin A (**2**), quercetin-3-O-*β*-D-glucopyranoside (**3**), (*E*)-*p*-coumaric acid (**4**), eugenol (**5**), eugenol, 1-acetate (**6**), chiakine (**7**), hexancosan-1',26'-dioate of bis[(2*S*), 2,3-dihydroxypropyl] (**8**), oleanolic acid (**9**), betulin (**10**), hopan-29-ol (**11**), hopan-30-ol (**12**), 22-hydroxyhopan-3-ol (**13**), and lupeol (**14**). These compounds were all isolated from the fruit of *Albizia lebbeck*. Only lebbeckisoetin A (**2**) and chiakine (**7**) were previously evaluated for their experimental antimicrobial activities, which both revealed potent antifungal activities. The virtual screening of the antifungal activity was performed on Maestro Schrödinger software using sterol 14-alpha demethylase (CYP51) from *Candida albicans* in complex with the tetrazole-based antifungal drug candidate VT1161 (VT1) (PDB Id: **5TZ1**) and sterol 14-alpha demethylase (CYP51) from the pathogenic yeast*Candida albicans* in complex with the antifungal drug posaconazole (PDB Id: **5FSA**). This is the first docking study of natural compounds using these**5TZ1** and **5FSA** as proteins. Compounds (**1-10**) reveal interesting binding strength with both **5TZ1** and **5FSA** proteins, with a docking score ranging from -7.892 to -5.256, supporting the experimental results. In addition, compounds (**1-9**) were

mostly active due to the formation of π-π interactions, H-bonds, and hydrophobic interactions, as well as π-cation and salt bridge interactions with both **5TZ1** and **5FSA**.

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1. Introduction

The development of new computational and experimental techniques, which are efficient, fast, and accurate, has become a priority for researchers in all domains around the world. The development of high-performance computers with great capacities has led computers to be used in both experimental and theoretical research. Nowadays, almost all research areas have both experimental and theoretical parts. This has shifted the paradigms in drug discovery. Most often, theoretical research is faster than experimental research and is used to either predict or support the experimental results (**Santamouris et al. 20012; Chen et al. 2015; Afshari and Muratçobanoğlu, 2023; Muhammed and Aki-Yalcin, 2024**. Nowadays, the modelization/production of new drugs is an easy task. However, the challenge incurred for this development is not long and tedious like two decades ago because the targeted drug is firstly designed in a computer and then suggested for molecular docking in order to better predict the ligand-receptor interactions. The term for the computational schemes that attempt to search for the “best” atomic coordinates/connectivity or bound association between two complex molecules is known as “docking” (**Ghasemi et al. 2017**). Docking study is a multidisciplinary science that is applied in a wide range of areas, particularly in drug discovery (**Sultana et al. 2024**). The prediction with a reasonable accuracy of the binding affinity between the ligand(s) and the protein is crucial in drug discovery and helpful in the optimization of the compound to establish a perfect connectivity with the targeted protein (**Rezaei et al. 2020; Sultana et al. 2024**). Molecular docking or computational simulation drug design calls upon the calculation of the binding strength between ligand and the protein which are two biological homologs. This manuscript deals with the computational investigation of some naturally isolated compounds against *C. albicans*. Therefore, the most prevalent human yeast pathogen is *C. albicans* because it is always present in the entire mammalian life cycle (**Hargrove et al. 2017**). The

cytochrome P450 enzyme [Sterol 14*α*-demethylase (CYP51)] is the required enzyme used by eukaryotic cells in steroidal biosynthesis and is mostly targeted by antifungal clinical drugs (**Hargrove et al. 2017**). CYP51 is an interesting subject for fundamental studies of P450. CYP51 is a great practical importance as a drug target. Sterol 14α-demethylase activity blocks sterol biosynthesis, influencing endogenous cholesterol production processes in animals. CYP51 inhibitors are being studied as potential cholesterol-lowering drugs and herbicides, it is noted that they are largely used as fungicides (**Lepesheva and Waterman, 2007; Lepesheva and Waterman, 2011; Scalese et al. 2024**). Quericitrin (**1**), lebbeckisoetin A (**2**), quercetin-3-O-*β*-D-glucopyranoside (**3**), (*E*)-*p*-coumaric acid (**4**), eugenol (**5**), eugenol, 1-acetate (**6**), chiakine (**7**), hexancosan-1',26'-dioate of bis[(2*S*), 2,3-dihydroxypropyl) (**8**), oleanolic acid (**9**), betulin (**10**), hopan-29-ol (**11**), hopan-30-ol (**12**), 22-hydroxyhopan-3-ol (**13**), and lupeol (**14**) (Figure 1) were all isolated from the fruit of*Albizia lebbeck*. Unfortunately, only lebbeckisoetin A (**2**) and chiakine (**7**) were evaluated for their experimental antimicrobial activities. The antimicrobial activities of lebbeckisoetin A (**2**) and chiakine (**7**) were assayed against five microbial strains (fungal: *Candida albicans*, and bacteria: *Pseudomonas aeruginosa, Enterococcus faecalis, Escherichia coli,* and *Staphylococcus aureus*) (**Leutcha et al. 2022**). This theoretical study was undertaken in the framework to support and better understand the experimental results at the atomic level, and to expand the antimicrobial assays of the other compounds reported from *Albizia lebbeck* that were not tested experimentally. The virtual screening of the antimicrobial activity performed on the crystal structure of sterol 14-alpha demethylase (CYP51) from *Candida albicans* in complex with the tetrazole-based antifungal drug candidate VT1161 (VT1) (PDB Id: **5TZ1**) and the crystal structure of sterol 14-alpha demethylase (CYP51) from a pathogenic yeast *Candida albicans* in complex with the antifungal drug posaconazole (PDB Id: **5FSA**) with natural compounds isolated from the fruit of*Albizia lebbeck* have shown promising antimicrobial results. This is the first docking study using natural compounds as ligands with the **5TZ1** and **5FSA** proteins. In addition, this survey has exhibited promising antifungal activities most of the docked compounds against *Candida albicans*.

2. Materials and Methods

2.1. *General Experimental Procedures*

The technical characteristics of the spectroscopic and spectrosmetric machines, as well as the experimental antifungal assays of the studied compounds, were already reported by **Leutcha et al. (2022)**. ChemDraw 16.0 software was used for the firstly used to draw the study compounds and secondly in the preparation of the docked ligands, while Schrödinger 4.2.1 software (Maestro 4.2.1) was used for the second preparation of the ligands and for the final docking.

2.2. *Plant Material, Extraction and Isolation, and Experimental Characterization*

A. lebbeck dry fruits were sampled in 2018 in Maroua city and identified by comparison with voucher specimen 58964/NHC in the Cameroon herbarium. The secondary metabolites theoretically studied here were all obtained from the fruits of *Albizia lebbeck,* a plant species of the Fabaceae family. The experimental antifungal assays, as well as all the reported compounds in this study, were obtained as previously reported by **Leutcha et al.** (**2022**).

2.3. *Docking Material*

The *in silico* docking investigation was performed in order to have a better view and understanding of the binding interaction strength between the natural ligands and the proteins at the atomic level. So, the 3D crystal complex structures of the two proteins were directly downloaded from the Protein Data Bank (PDB) website. The crystal structure of sterol 14-alpha demethylase (CYP51) from *Candida albicans* in complex with the tetrazole-based antifungal drug candidate VT1161 (VT1) (PDB Id: **5TZ1**) and the crystal structure of sterol 14-alpha demethylase (CYP51) from the pathogenic yeast *Candida albicans* in complex with the antifungal drug posaconazole (PDB Id:**5FSA**) were used as proteins. The structures of the isolated compounds were firstly drawn and prepared in the "MDL SDfile V3000 (*.sdf)" format using ChemDraw 16.0. Secondly, the software Maestro Schrödinger 4.2.1 *Ligprep* module was used for the preparation of ligands. A receptor grid was generated around the co-crystallized ligands for both proteins, and the ligands were docked using the glide XP module. In addition, the protein preparation wizard was used for the protein preparation and minimization as reported by Zafar et al. (2023). Finally, to visualize and better understand the ligand-protein binding effects, the 3D and 2D docked poses were captured and examined.

2.4. *Experimental Antimicrobial Assay*

The experimental antimicrobial activities of lebbeckisoetin A (**2**) and chiakine (**7**) were performed as reported by **Leutcha et al.** (**2022**) (Table S1). The microbial strains were collected from the American Type Culture Collection (ATCC): one yeast, *Candida albicans* ATCC 9028, and four bacteria: *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 1026), *Enterococcus faecalis* (ATCC 29212), and *Pseudomonas aeruginosa* (ATCC 74117) (Table S1).

3. Results and Discussion

Computational or molecular docking drug design calls upon the calculation of the binding strength between two biological homologs, which are ligands and proteins. This manuscript deals with the computational investigation of some naturally isolated compounds. Therefore, quercitrin (**1**), lebbeckisoetin A (**2**), quercetin-3-O-*β*-D-glucopyranoside (**3**), (*E*)-*p*-coumaric acid (**4**), eugenol (**5**), eugenol, 1-acetate (**6**), chiakine (**7**), hexancosan-1',26'-dioate of bis[(2*S*), 2,3-dihydroxypropanone) (**8**), oleanolic acid (**9**), betulin (**10**), hopan-29-ol (**11**), hopan-30-ol (**12**), 22-hydroxyhopan-3-ol (**13**), and lupeol (**14**) (Fig. 1; Table 1) were all isolated from the fruit of*Albizia lebbeck*. From all the above-listed compounds, only lebbeckisoetin A (**2**) and chiakine (**7**) were experimentally assayed for their antimicrobial activities against five microbial strains (one fungal: *Candida albicans* and four bacterial: *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Enterococcus faecalis*) (Table S1) (**Leutcha et al. 2022**); the reason being the least quantities of most of the isolated compounds. This theoretical study was undertaken in the framework to support and better understand the experimental results at the atomic level, and to expand the antimicrobial assays of the other compounds reported from *Albizia lebbeck* that were not tested experimentally.

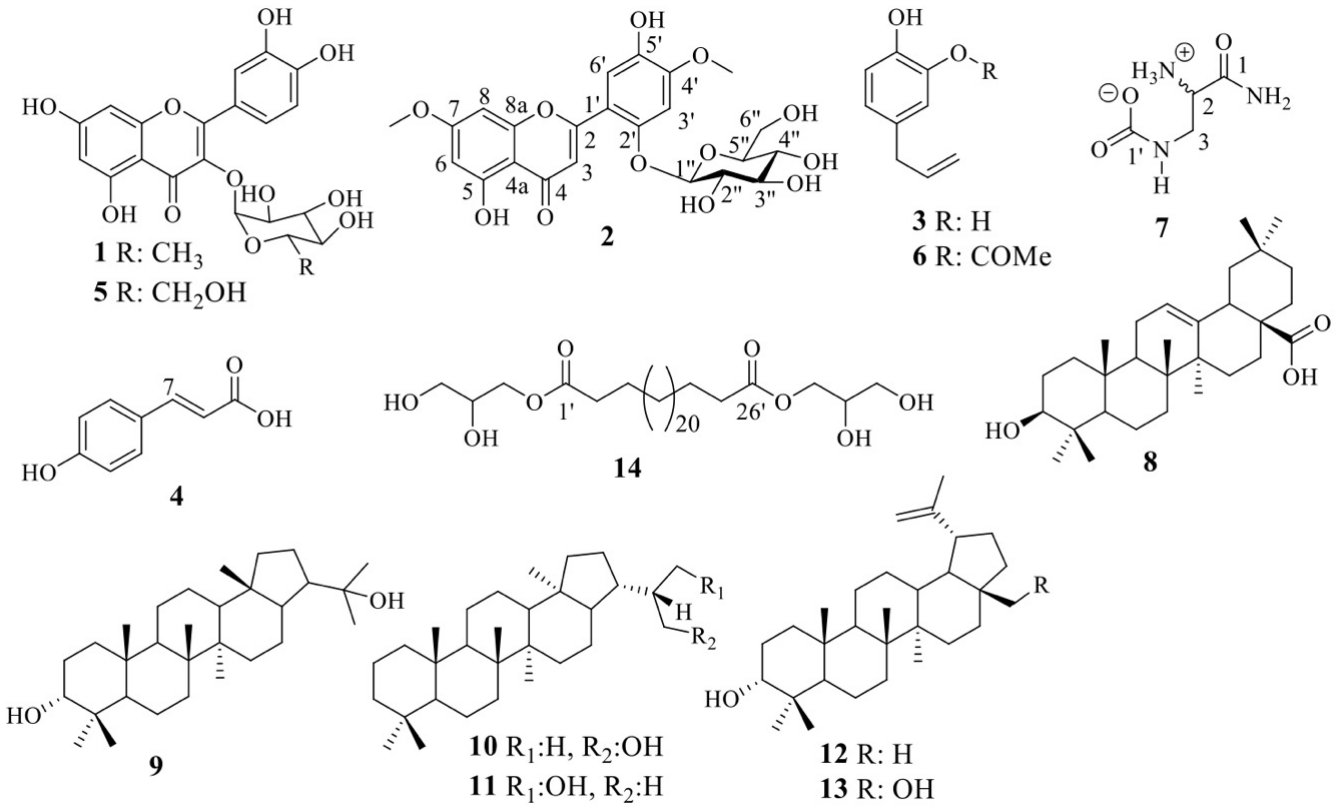
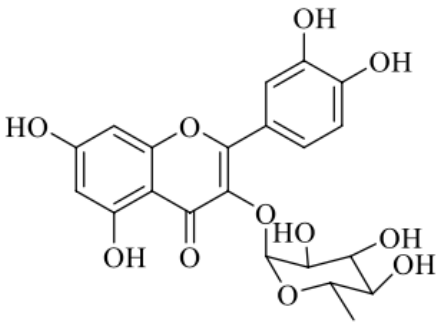
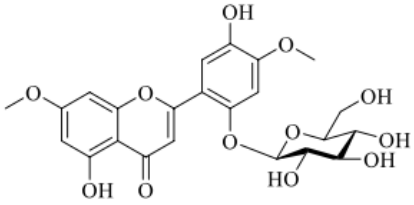
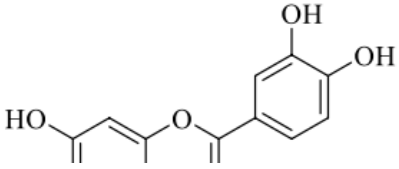
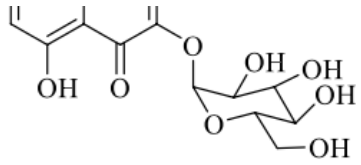
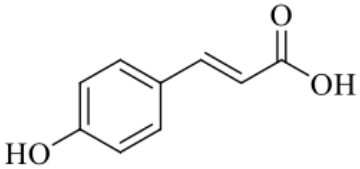
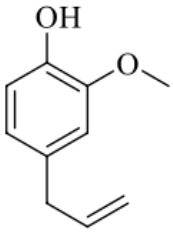
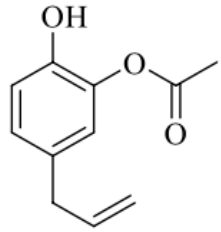
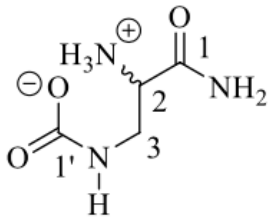
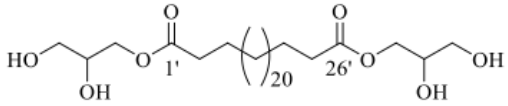
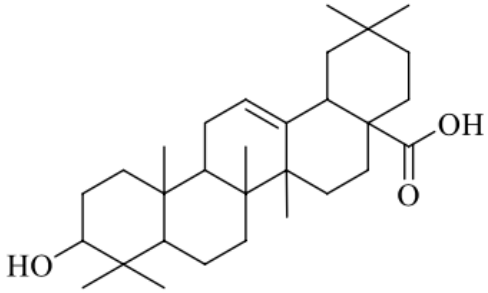


Figure 1. Structures of the docked compounds **1-14**

Docked compounds and name	Docking score for 5TZ1	Docking score for 5FSA	Experimental result against *Candida albicans* ATCC 9028
 Quericitrin (**1**)	-7.892	-7.923	Not tested
 Lebbeckisoetin A (**2**)	-7.815	-7.756	Tested with MIC value of 32 μg/mL
		-7.717	Not tested

 Quercetin-3-O-β-D-glucopyranoside (**5**)	-5.528		
 (*E*)-*p*-coumaric acid (**4**)	-5.786	-5.635	Not tested
 Eugenol (**3**)	-5.947	-5.717	Not tested
 Eugenol, 1-acetate (**6**)	-5.056	-5.256	Not tested
 Chiakine (**7**)	-3.516	-5.273	Tested with MIC value of 32 μg/mL
 Hexancosan-1',26'-dioate of bis[(2s), 2,3-dihydroxhpronane) (**14**)	Docking score less than -2	-7.425	Not tested
 Oleanolic acid (**8**)	Docking score less than -2	-5.923	Not tested
			

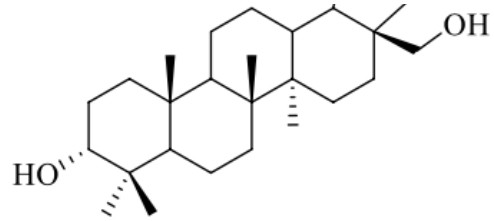
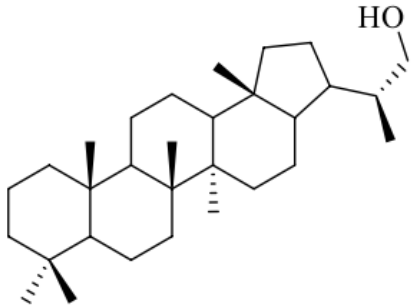
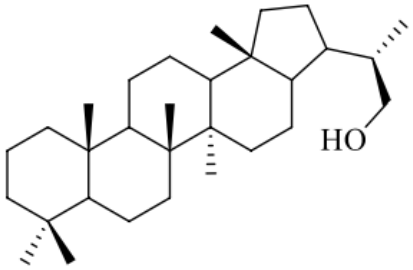
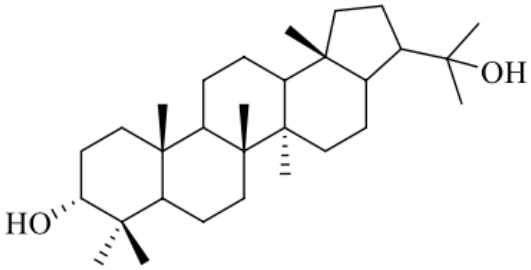
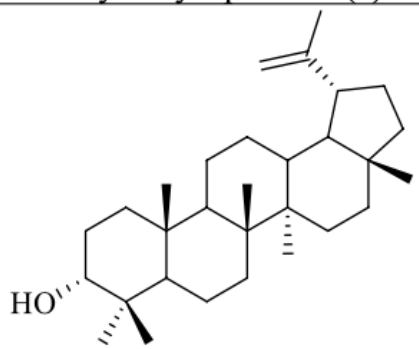
 Betulin (**13**)	Docking score less than -2	-5.906	Not tested
 Hopan-29-ol (**10**)	Docking score less than -2	Docking score less than -2	Not tested
 Hopan-30-ol (**11**)	Docking score less than -2	Docking score less than -2	Not tested
 22-hydroxyhopan-3-ol (**9**)	Docking score less than -2	Docking score less than -2	Not tested
 Lupeol (**14**)	Docking score less than -2	Docking score less than -2	Not tested

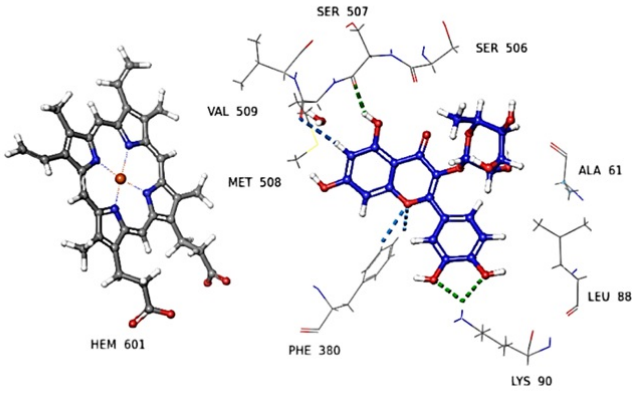
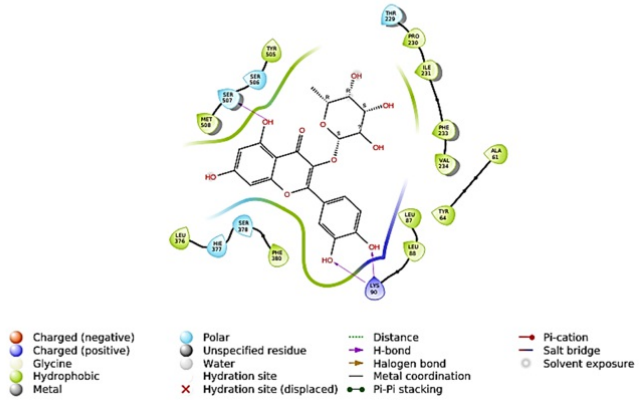
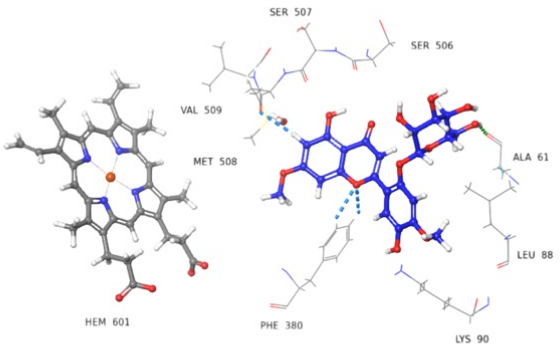
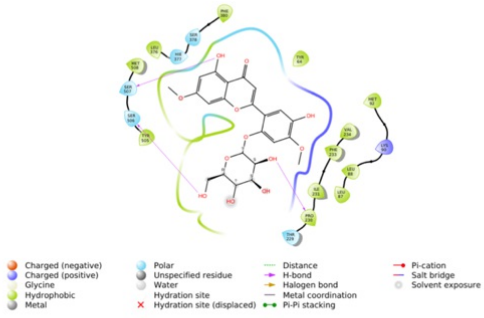
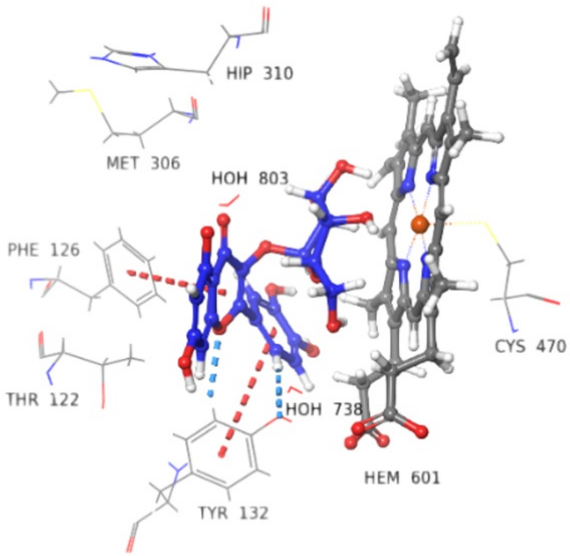
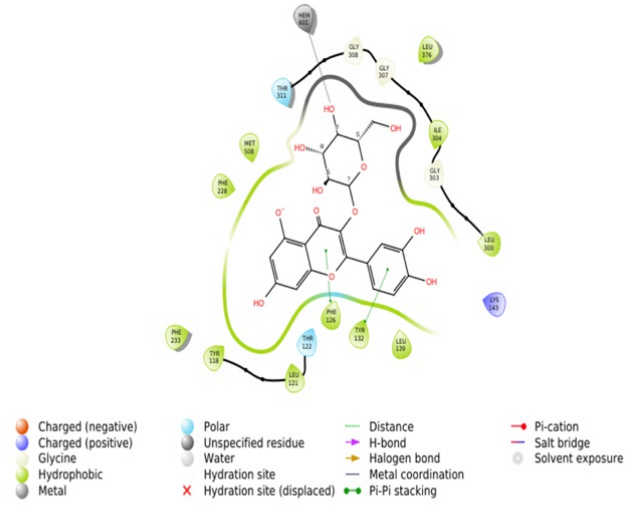
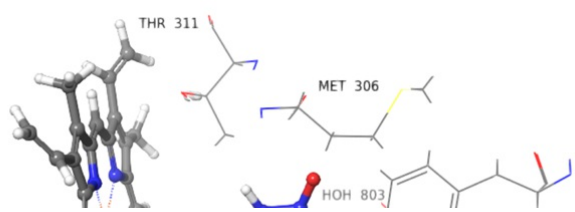
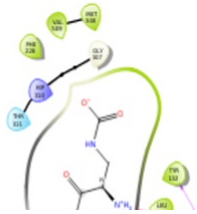
Table 1. Docking scores of **5TZ1** and **5FSA**. Tested yeast: *Candida albicans* ATCC 9028; Minimum Inhibitory Concentration (MIC); PDB ID: **5TZ1** (Title: Crystal structure of sterol 14-alpha demethylase (CYP51) from *Candida albicans* in complex with the tetrazole-based antifungal drug candidate VT1161 (VT1)); PDB ID: **5FSA** (Title: Crystal structure of sterol 14-alpha demethylase (CYP51) from a pathogenic yeast *Candida albicans* in complex with the antifungal drug posaconazole).

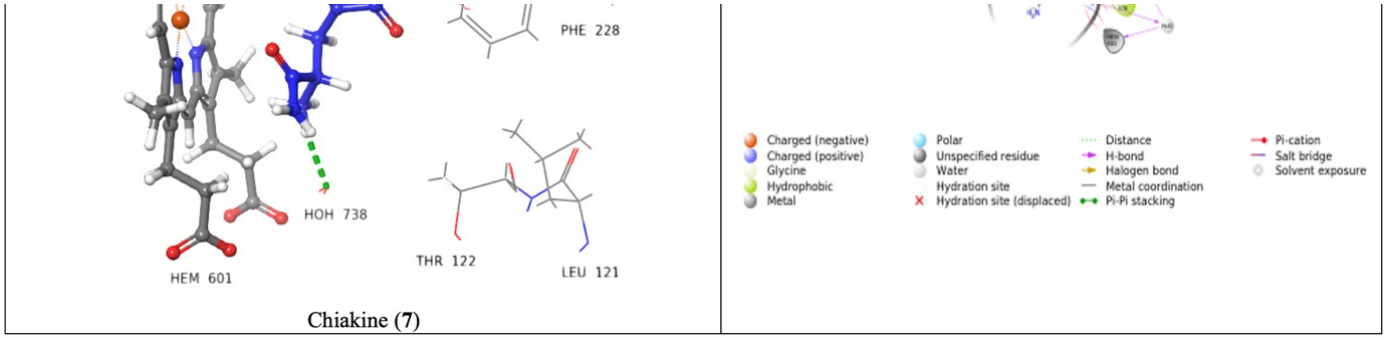
This experimental survey has exhibited promising antifungal activities of the two naturally isolated compounds against *Candida albicans* with an MIC value of 32 μg/mL (**Leutcha et al. 2022**). On the other hand, the most prevalent human yeast pathogen is *C. albicans* because it is always present throughout the entire mammalian life cycle (**Hargrove et al. 2017**). The cytochrome P450 enzyme [Sterol 14α-demethylase (CYP51)] is the required enzyme used by eukaryotic cells in steroidal biosynthesis and is mostly targeted by antifungal clinical drugs (**Hargrove et al. 2017**). The X-ray crystal structure of *Candida albicans* CYP51 as a suitable complex agent for a docking study was previously reported by Hargrove et al. (**2017**). This is the first docking study performed on the **5TZ1** and **5FSA** proteins using natural compounds as ligands. However, these two proteins were targeted for their *in silico* and *in vitro* antifungal activities against *C. albicans* (CYP51) (**Gandham et al. 2024; Emami et al. 2023; Prakash & Kabir, 2022; Silva et al. 2022; Sari Kart, 2020; Lebouvier et al. 2020**).

Before docking, the most stable conformation of the docked compounds was firstly searched, and after docking, some poses were also captured to better explain the ligand-protein interactions. Compounds (**1**-**14**) were docked for their antifungal potencies against the sterol 14-alpha demethylase (CYP51) from *Candida albicans* in complex with the tetrazole-based antifungal drug candidate VT1161 (VT1) (PDB Id: **5TZ1**) and sterol 14-alpha demethylase (CYP51) from the pathogenic yeast *Candida albicans* in complex with the antifungal drug posaconazole (PDB Id:**5FSA**). Compounds (**1**-**10**) reveal interesting docking scores ranging from -7.923 to -3.516, while compounds (**11**-**14**) reveal docking scores less than -2 on the two proteins (**5TZ1** and **5FSA**) (Table 2 and S2). Generally, phenolic compounds were more potent, which may be due to their capacity to form H-bonds, aromatic interactions, π-πinteractions, and hydrophobic interactions, while other compounds were forming H-bonds, salt bridges, and hydrophobic interactions. In addition, quericitrin (**1**) (-7.892 and -7.923), lebbeckisoetin A (**2**) (-7.815 and -7.756), and quercetin-3-O-β-D-glucopyranoside (**3**) (-5.528 and -7.717), which are all flavonoids, were the most active compounds against **5TZ1** and **5FSA**, respectively (Table 1, 2, and S2). Compound (**1**) reveals at the atomic level the formation of H-bonds with Lys 90 and Ser 507, aromatic interactions with H_2O 2045, Hie 377, Phe 380, and Val 509 and π-π interactions with Phe 380, while compound (**2**) have established H-bonds with Lys 90, Ala 61, Ser 506, Ser 507, and Pro 230; aromatic interaction with Phe 233, Phe 380, and Met 508; and a π-π interaction with Phe 233, and compound (**3**) was establishing H-bonds with Lys 90, Ser 507, Pro 210, and Leu; aromatic interactions with Phe 380 and Tyr 132, and π-π interactions with Hie 377, Tyr 132, and Phe 126, and a metallic connection with HEM 601 (heme group), which supports their high docking scores. These results are in agreement with the experimental results assayed on the *C. albican* fungal strain. The interesting *in silico* and *in vitro* potencies of flavonoids against *C. albican* are not amazing. According to **Silva et al.** (**2022**), flavonoids are reported to have potent antifungal activities against *C. albican* with interesting docking scores. The moderate activities of eugenol derivatives (compounds **5** and **6**) against the sterol 14-alpha demethylase (CYP51) of *C. albican* were in agreement with the reported data of **Lima et al.** (**2020**). Among all the non-phenolic compounds, hexancosan-1',26'-dioate of bis[(2*S*), 2,3-dihydroxypropyl)] (**8**) has revealed the most interesting docking score of -7.425 on **5FSA**; this might be due to its capacity to form a large number of H-bonds (H-bonds with Hie 120, ALA 117, Asp 225, Asp 502, Ser 507, Gly 303, and Pro 503). On the other hand, chiakine (**7**) was the only compound that established the salt bridge with Leu 124, Tyr 183, H_2O 803, and HEM 601 at the atomic level, with a docking score of -5.273 on **5FSA**. This might be due to its amphionic structure.

From the above mentions, it appears that **5FSA** was more interactive with all the docked ligands as compared to**5TZ1**.

Docking pictures FOR 5TZ1

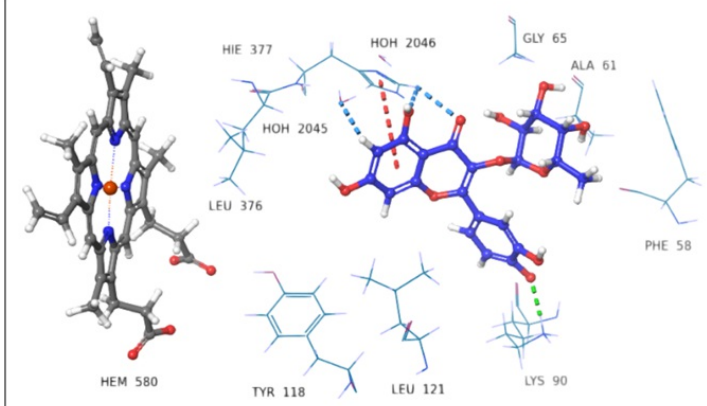
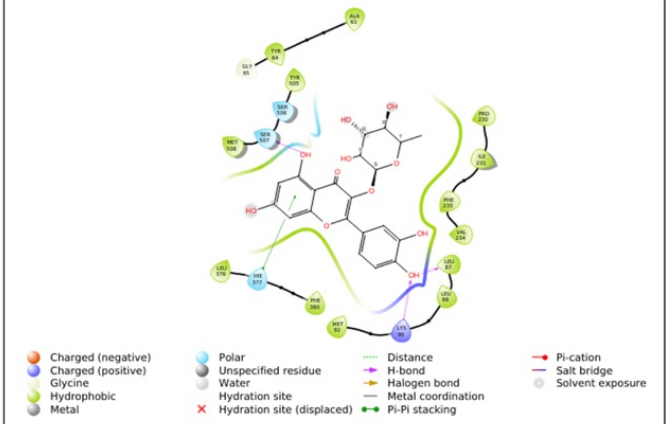
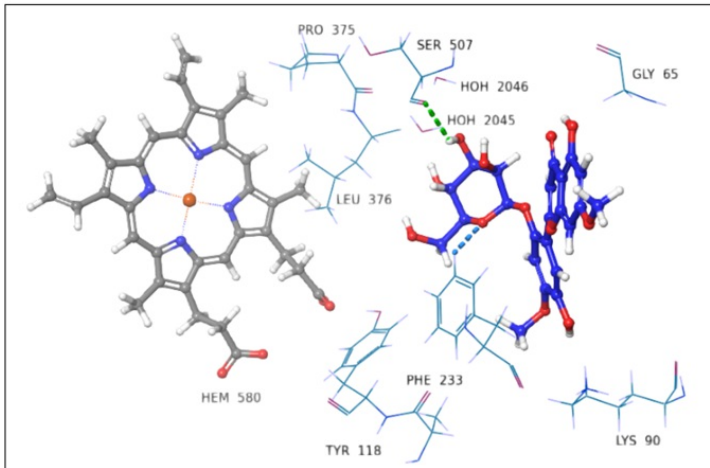
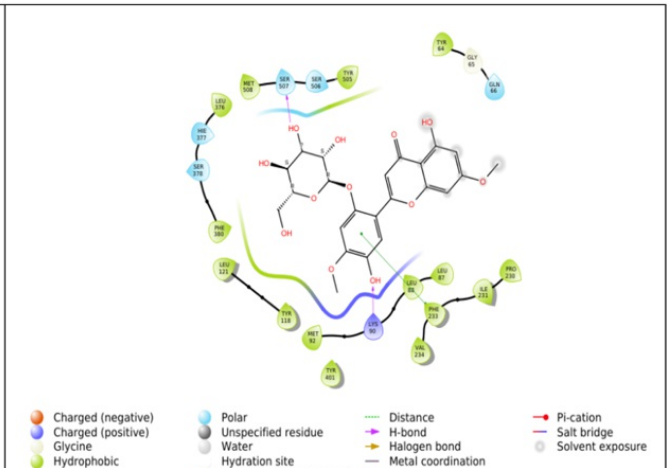
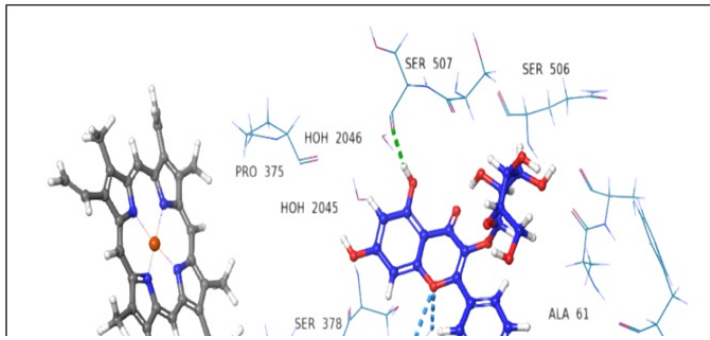
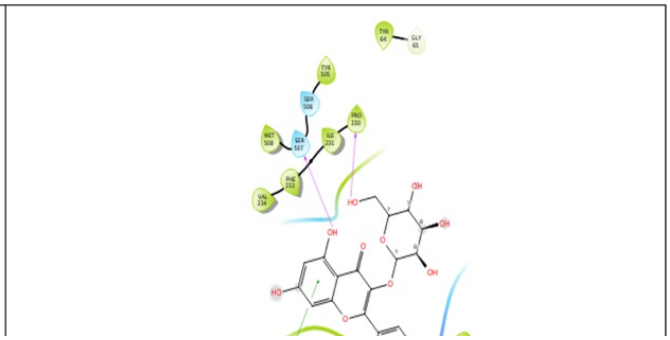
3D	2D
 Quericitrin (**1**)	
 Lebbeckisoetin A (**2**)	
 Quercetin-3-O-*β*-D-glucopyranoside (**3**)	
	



Chiakine (**7**)

Table 2a. Interaction between ligands and proteins (**5TZ1** and **5FSA**)

Docking pictures FOR 5FSA

3D	2D
	
Quericitrin (**1**)	
	
Lebbeckisoetin A (**2**)	
	

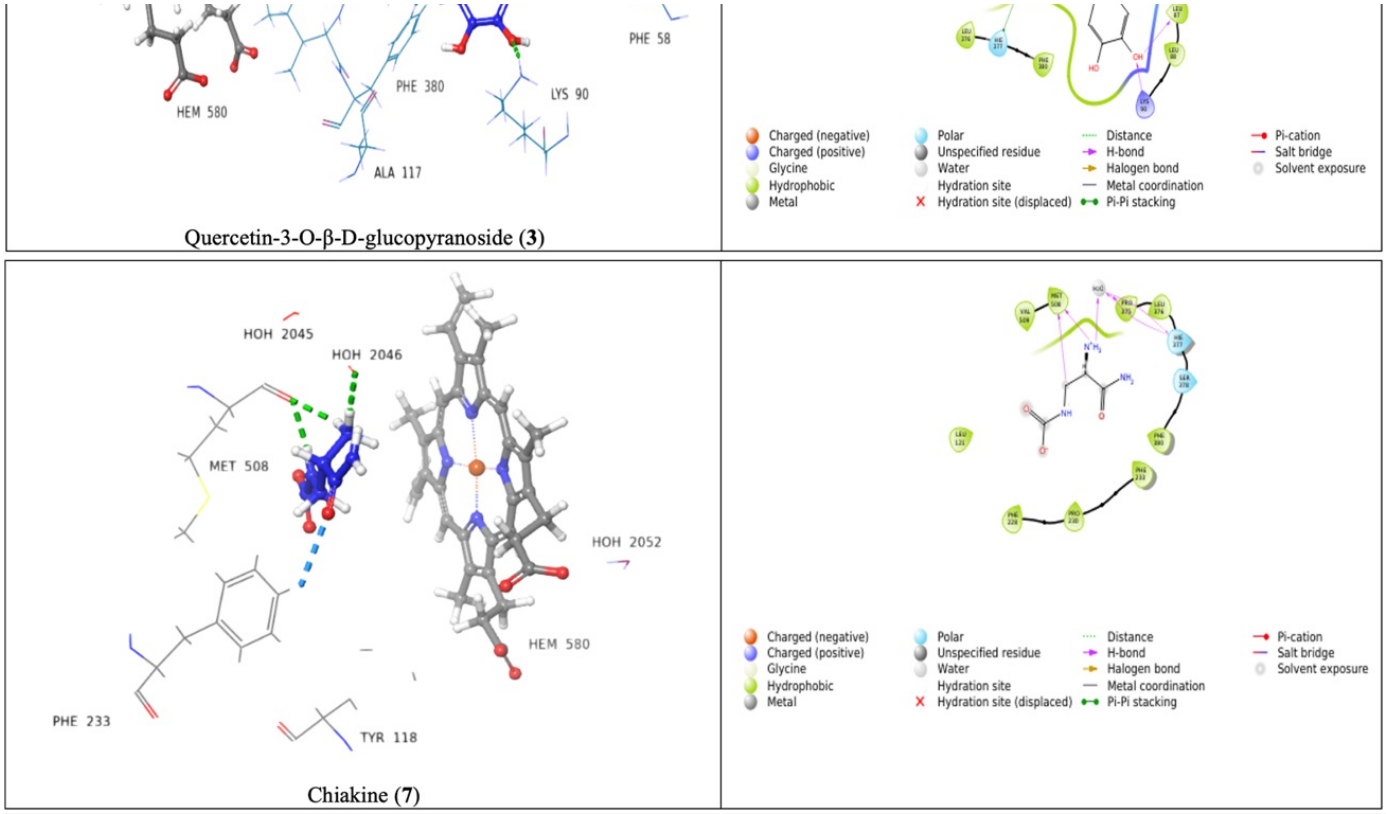


Table 2b. Interaction between ligands and proteins (**5TZ1** and **5FSA**)

Like previous theoretical investigations undertaken on the above-listed compounds, we can report, to the best of our knowledge, that Quercitrin (**1**) was previously suggested for a docking study of its antioxidant capacity (**Peng et al. 2023**), while quercetin-3-O-*β*-D-glucopyranoside (**3**) was docked for its acetylcholinesterase activity (**Hamdani et al. 2020**) and for its inhibitory effects on human UDP-glucuronosyltransferase 1A isoforms (**Zhang et al. 2021**). Eugenol derivatives (**5** and **6**) were studied for their *in silico* potencies against breast cancer (**Rasul et al. 2022**), dynamic molecular simulation of antioxidant and antimicrobial activities (**Abdou et al. 2022**), and antifungal activity against *C. albicans* (**Lima et al. 2020**). Additionally, (*E*)-*p*-coumaric acid (**4**) was evaluated for its *in silico* and *in vitro* antibacterial and anticancer activities against lung cancer cell lines (**Sathish et al. 2017**), murine leukemia cell lines (**Soekamto et al. 2021**), antiparasitic activities against *Plasmodium falciparum* and *Leishmania braziliensis* (**Lopes et al. 2020**), type 2 diabetes, inflammatory, and *α*-amylase activities (**Huang et al. 2023**). Oleanolic acid (**9**) was theoretically assayed for its inhibitory effect on N-myristoyl transferase towards antifungal agents (**Guerrero-Perilla et al. 2015**) and protein-Tyrosine phosphatase 1B (**Ghosh et al. 2018**), and for its potential to alleviate osteoporosis (**Wu et al. 2021**). While lupeol (**14**) was docked for its inhibitory antifungal potential on the CYP51 enzyme (**Hassan et al. 2022**), on cancer (such as Topoisomerase, Caspase-3, PTK, BCL-2, mTOR, PI3K, H-Ras, and AKT) (**Gunasekaran at al. 2022**), on its Alzheimer potency (**Koirala et al. 2017**), on mouse skin fibrosarcoma (WEHI-164) and human gastric carcinoma (AGS) cell lines (**Ghoran et al. 2020**), and on breast cancer (ER-α and HER2) (**Pratama, 2018**). And, betulin (**10**) was *in vitro* and *in silico* investigated for its antiproliferative effect against lung carcinoma (A549), human leukemia (CCRF/CEM and MV-4-11), melanoma (Hs 294T), prostate cancer (DU 145), and murine leukemia P388 cell lines (**Chrobak et al. 2019**) and also evaluated for its *in vitro* cytotoxic activity against human cancer cell lines (glioblastoma (SNB-19), amelanotic melanoma (C-32), and two breast cancers (MDA-MB-

231 and T47D) (**Chrobak et al. 2021**)), on a series of monkeypox and SARS-CoV-2 proteins (**Burkhanova et al. 2022**), and for its alpha-glucosidase and alpha-amylase inhibitory activities (**Gurupriya and Cathrine, 2021**). To the best of our knowledge, this is the first docking investigation undertaken on lebbeckisoetin A (**2**), chiakine (**7**), hexancosan-1',26'-dioate of bis[(2*S*), 2,3-dihydroxypropyl) (**8**), hopan-29-ol (**11**), hopan-30-ol (**12**), and 22-hydroxyhopan-3-ol (**30**).

Indeed, the virtual screening of the antimicrobial activity performed on the crystal structure of sterol 14-alpha demethylase (CYP51) from *Candida albicans* in complex with the tetrazole-based antifungal drug candidate VT1161 (VT1) (PDB Id: **5TZ1**) and the crystal structure of sterol 14-alpha demethylase (CYP51) from a pathogenic yeast *Candida albicans* in complex with the antifungal drug posaconazole (PDB Id: **5FSA**) or natural compounds isolated from the fruit of *Albizia lebbeck* has shown promising antimicrobial results. In addition, this is the first docking of natural compounds used as ligands with the **5TZ1** and **5FSA** proteins.

4. Conclusion

The aim of this research was the computational investigation of the naturally isolated compounds against *C. albicans*, which is the most prevalent human yeast pathogen. This theoretical study was undertaken in the framework to better understand the previous experimental results. So, the antifungal performed using **5TZ1** and **5FSA** as protein with fourteen natural compounds (**1**-**14**) reported from *Albizia lebbeck* was in agreement with the experimental results.

Statements and Declarations

Conflicts of Interest

No financial or conflict of interests are declared by the authors.

Authors' Contributions

Peron Bosco Leutcha conceptualized the study; Peron Bosco Leutcha and Humaira Zafar, methodology; Peron Bosco Leutcha, original draft preparation; Peron Bosco Leutcha, Serges Honoré Ediah Ngalaha, Humaira Zafar, Muhammad Iqbal Choudhry, Alain Meli Lannang, supervision, editing, and review.

Data Availability

In the supplementary material, 2D and 3D poses of docking are available.

Supplementary Materials

In the supplementary material, 2D and 3D poses of docking are available.

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