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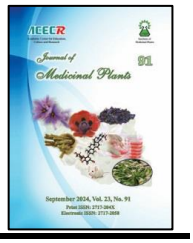

Research Article

Antifungal potential of the main compounds of *Cuminum cyminum* L. in targeting secreted aspartyl proteinase of *Candida albicans* compared to fluconazole

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ABSTRACT

Background: *Candida albicans* is naturally present in the normal human flora. This microorganism changes into an opportunistic fungus due to imbalances in microbiome composition, especially in an impaired immune system condition. The few available antifungal classes, severe toxicity, side effects, high cost, and the emergence of drug resistance are some of the limitations that physicians have in prescribing antifungal drugs**. Objective:** The current research aims to study the antifungal potential of the main compounds of *Cuminum cyminum* L. in inhibiting secreted aspartyl proteinase of *C. albicans* compared to fluconazole. **Methods:** In silico techniques were employed in this study. The main biochemicals of *C. cyminum* were obtained and optimized. 2D and 3D structures of chemical compounds were retrieved from the ChemSpider database and HyperChem software respectively. Auto Dock Vina and Discovery Studio 2024 Client were done to detect the potent inhibitor against the enzyme's active site. Finally, the physicochemical and toxicity properties of inhibitors were obtained. **Results:** The results of Auto Dock Vina indicated that Apigenin-7-O- glucoside has 80 percent similarity with fluconazole in the potential inhibition and exhibited a high free binding energy (ΔGbind: -10.48 kcal/mol). 13 amino acid residues involved in the interaction between best ligand and receptor that are Thr221, Asp32, Asp218, Asp86, Gly34, Ile123, Tyr84, Gly85, Ile30, Ser35, Ala119, Ile216, and Lys193. **Conclusion:** The present study affirmed that Apigenin-7-O- glucoside in *C. cyminum* could be a promising inhibitor against secreted aspartyl proteinase. However, there is still a need for clinical future investigations to support these findings.

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; EC, Enzyme Commission number; PDB, Protein Data Bank; MW, Molecular weight; TPSA, Topological Polar Surface Area; NHA, Number of Hydrogen Bond Acceptors; NHD, Number of Hydrogen Bond donors

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1. Introduction

Candida albicans is a member of the normal microbiota and live in various tissues such as oral mucosa, skin, vagina, and gastrointestinal tract [1]. *C. albicans* is classified as an opportunistic fungus. Disturbing the host's immune balance, staying in long-term stress, changing the resident microbiota, and other factors can lead to excessive proliferation of this microorganism and cause a wide range of fungal infections from superficial mucus to candidiasis [1, 2]. Fungal infections kill about 1.7 million people worldwide annually [1]. The similarity of the cell structure of fungi to eukaryotic cells becomes an obstacle to the development of antifungal drugs. In recent years, the increase in the number of patients with fungal infections, the high cost of antifungal drugs, shortcomings, and toxicity of the available antifungal drugs, and resistance to treatment are some of the serious problems related to fungal infection [3, 4]. In traditional medicine, a wide range of plant extracts as natural medicines with antimicrobial and antifungal properties have been introduced, and trying to find herbal alternatives with similar or better properties than chemical compounds can help solve the problems of antifungal drugs [1, 5].

Cuminum cyminum L. is an edible herbal plant belonging to the family *Apiaceae* that is locally known as "zeera" [6]. The extract of this plant contains substances of many strong bioactives and biochemicals, including alkaloids, flavonoids, and terpenoids *C. cyminum* has immense pharmacological potential such as anti-inflammatory, antibacterial, antioxidant, antiviral, and antifungal activity. Furthermore, antidiabetic effects, anticarcinogenic effects, hypotensive effects, cardio-protective influence, hypolipidemic and weight reduction effects, miscellaneous nutraceutical effects, and chemopreventive effects are listed as its clinical users [6, 7]. Cuminaldehyde has been reported as its main bioactive substance which has long been used as a therapeutic agent [8].

C. albicans has a complex interaction with the host through the cell wall and a unique pathogenic strategy. One of the most important enzymes in fungal pathogenicity is secreted aspartic proteases (EC.3.4.23) [9, 10]. These extracellular hydrolytic enzymes belong to the endopeptidase family with high activity at acidic pH and are encoded by a multigene family with at least ten different genes. To invade and destroy host cells and proteins, *C. albicans* use this enzyme. Secreted aspartic proteases digest the proteins by hydrolysis of peptide bonds. secreted aspartic proteases not only play a key role in the infection process but they are also critical for yeast survival. For this reason, aspartyl proteinase inhibitors are used as antifungal and antibiofilm agents in treating *C. albicans* infections. By inhibiting the activity of secreted aspartic proteases, critical steps in fungal pathogenesis such as adhesion, hyphal formation, biofilm development, host invasion, and immune evasion can potentially be disrupted [9-11].

Considering the limitations of the usual drugs in the treatment of fungal infections, it seems necessary to find new plant-derived natural compounds with antifungal properties and fewer side effects. In this research, we study the potential of the main compounds of *C. cyminum* in blocking the active site of the secreted aspartyl proteinase of *C. albicans* compared to Fluconazole.

2. Materials and Methods

2.1. Preparation of 2D and 3D structures of chemical compounds

According to the articles [12-15], ligands with the highest amount in *C. cyminum* L. were selected for investigation. 2D and 3D structures

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of chemical compounds were retrieved from the ChemSpider database and HyperChem Professional software respectively. ChemSpider is easily available as a free chemical structure database at https://www.chemspider.com. The 3D structures of the ligands were drawn based on carbon atoms in the HyperChem Professional software, subsequently, desired atoms were substituted for carbon atoms, and energy optimization was carried out by molecular mechanics optimization.

2.2. Selection and preparation of target protein

Based on the importance of the enzyme's role in the fungus's life, the absence of mutation, and the level of resolution in the crystal structure, the target protein was selected. The 3D crystal structure of the chosen protein in PDB format was downloaded from the protein data bank and transferred to the Discovery Studio 2024 software. To prepare the protein for docking analysis, unnecessary components such as water molecules, homologous polypeptide chains, and co-crystal parts were eliminated.

2.3. Grid center selection and docking protocol validation

Two important factors that must be considered before docking the ligands are determining the dimensions of the grid center and the grid box. Based on the active site amino acids, the grid center was selected by Discovery Studio 2024 software. To validate the docking procedure, the cocrystal ligand, pepstatin, was prepared for re-docking. After re-docking into the active site of secreted aspartic proteinase, Pepstein's structure was overlapped in two states before and after docking.

2.4. Autodock Vina analysis

A practical tool in computer-based drug design and discovery is the molecular docking approach. In this method, in silico technology is used to simulate interactions between the drug and the receptor. In our research, with AutoDock Vina, 3D structures of chemical compounds were docked to the active site of secreted aspartic proteinase to study the directions or situations in which compounds bind to the receptor, the binding affinity and amino acids involved in the ligand-receptor interactions. The Output files from AutoDock Vina were analyzed by GaussView 5.0 and Discovery Studio 2024 software.

2.5. Physicochemical Properties and Toxicity Predictions

The adverse properties of compounds in terms of physicochemical properties and toxicity are the main reasons for unsuccessful drug development. DMETlab 2.0 is a practical, and free database that helps in the systematic evaluation of in silico pharmacokinetic properties. For in silico physicochemical properties, we used ADMETlab 2.0. SMILES format of chemical compounds was obtained from ChemSpider and input to ADMETlab 2.0. The toxicity of the compounds was evaluated by in silico method using ProTox-II - Prediction in https://tox-new.charite.de/protox_II.

3. Results

3.1. Preparation of 2D and 3D structures of chemical compounds

The ChemSpider ID, molecular Formula, and 2D structures of chemical compounds namely *p*-cymene, γ-terpinene, cuminaldehyde, apigenin-7-O- glucoside, and fluconazole (positive control) that were retrieved from the database ChemSpider are shown in Table 1. Energy optimization of these compounds was done with RMS gradient of 0.1 kcal/(Å mol) in HyperChem Professional software.

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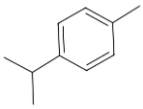
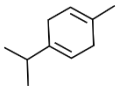
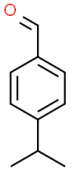
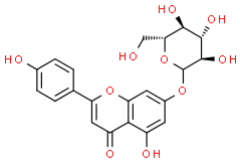
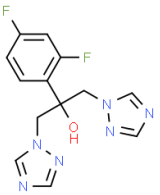
Table 1. Details of studied compounds

Number	ChemSpider ID	Name of chemical compounds	Molecular Formula	2D structures of chemical compounds
1	7183	*p*-cymene	$C_{10}H_{14}$	
2	7181	γ-terpinene	$C_{10}H_{16}$	
3	21106431	Cuminaldehyde	$C_{10}H_{12}O$	
4	18668699	Apigenin-7-O-glucoside	$C_{21}H_{20}O_{10}$	
5	3248	Fluconazole	$C_{13}H_{12}F_2N_6O$	

ID: Identity

3.2. Selection and preparation of target protein

Among *C. albicans* enzymes, one of the essential parameters in its pathogenicity is secreted aspartic proteinase. The 3D crystal structure of this enzyme with accession number: 2QZX, resolution: 2.50 Å, Mutation(s): No, Organism(s): *C. albicans*, EC: 3.4.23.24 in the protein data bank is available. For receptor preparation, in addition to removing water and cocrystal molecules, to facilitate the docking process, chain B was removed from the two homologous polypeptide chains in this protein. The prepared target protein with active site amino acids is depicted in Fig. 1.

3.3. Grid center selection and docking protocol validation

After overlapping two positions of pepstein's structure before and after docking, the best dimensions of the grid center and the grid box were detected. The dimensions of the grid center were 8.325, 26.312, and 24.608 for x, y, and z respectively. The grid box sizes were 12.16 x, 12.44 y, and 16.79 z. Superimposed structures are shown in Fig. 2.

3.4. Autodock Vina analysis

Binding affinities, number of bonds, and interacting residues for each compound were investigated by AutoDock Vina and Discovery

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Studio 2024 software. Molecular docking results of selected compounds of *C. cyminum* and fluconazole as positive control are shown in Table 2. The conformation of the best compound with the most negative binding energy was overlapped with the fluconazole in Fig. 3.

3.5. Physicochemical Properties and Toxicity Predictions

The results of physicochemical properties and toxicity predictions of studied compounds are presented in Table 3. Based on the data, our compounds follow the Drug-Like Soft rule and based on ProTox-II – Prediction, they are non-toxic.

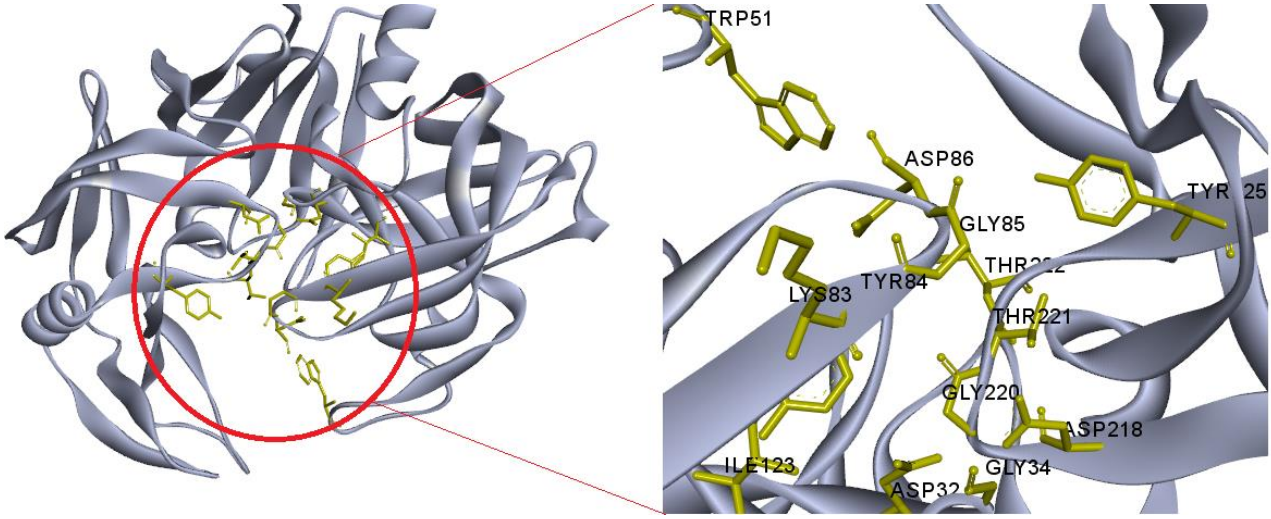

Fig. 1. The prepared secreted aspartic proteinase (PDB ID: 2QZX) with active site amino acids

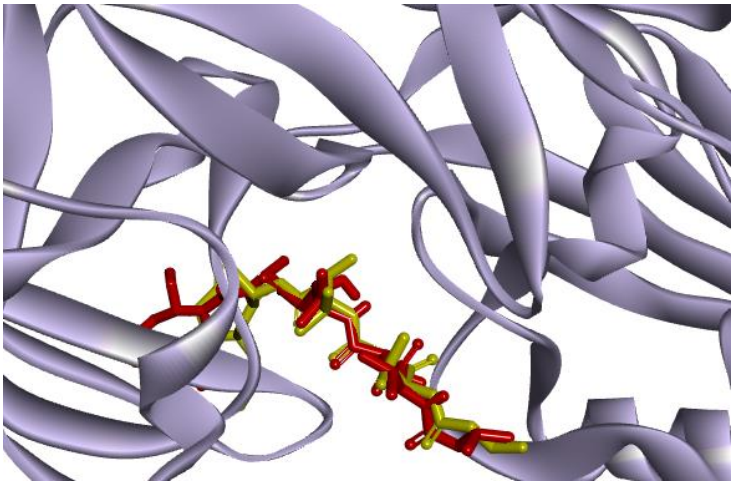

Fig. 2. Superimposed structure of pepstein before (yelow) and after docking (red)

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Table 2. Molecular docking results of selected compounds of *C. cyminum* and Fluconazole as positive control

Number	compounds	Binding affinities (kcal/mol)	number of residues involved in ligand-receptor interaction	residues involved in hydrogen bonds	residues involved in van der Waals and Electrostatic interaction	Binding similarities with Fluconazole (%)
1	*p*-cymene	-3.94	9	-	Thr221, Ile30, Gly220, Leu216,Gly85, Gly34,Ser35, Ile123, Tyr84	60 %
2	γ-terpinene	-4.73	8	-	Gly220, Thr221,Asp32,Asp218,Asp86, Gly34, Ile123, Ile30	70 %
3	Cuminaldehyde	-4.85	8	-	Gly220, Ile123,Asp32,Asp218,Asp86, Ile123, Tyr84, Ile305	70 %
4	Apigenin-7-O-glucoside	-10.48	13	-	Thr221,Asp32,Asp218,Asp86, Gly34, Ile123, Tyr84, Gly85, Ile30, Ser35, Ala119,Ile216,Lys193	80 %
5	Fluconazole (positive control)	-7.20	10	Gly220, Thr221	Asp218,Asp86, Gly34, Ile123, Tyr84, Gly85, Ile305,Asp32,	100 %

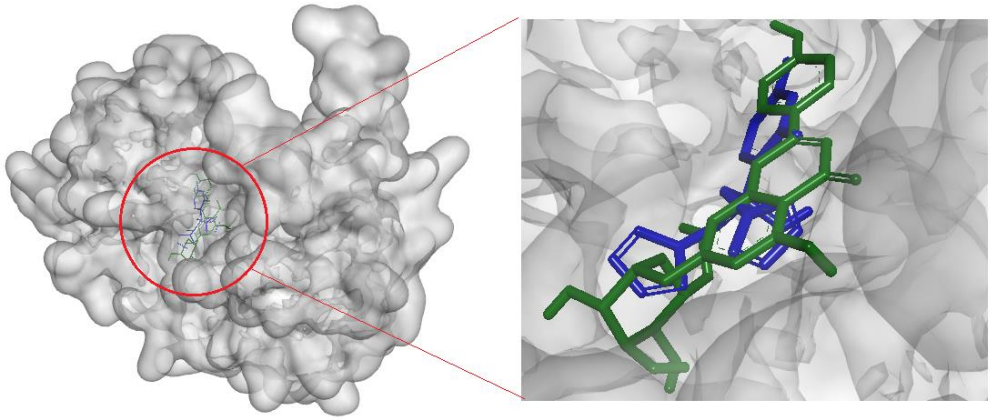

Fig. 3. Superimposed structure of Apigenin-7-O- glucoside (green) with Fluconazole as the positive control (blue)

Table 3. The results of physicochemical properties and toxicity predictions of compounds

Compounds	Molecular weight (g/mol)	NHA	NHD	TPSA	logP	logS	Toxicity Predictions			
							Hepatotoxicity	Carcinogenicity	Immunotoxicity	Cytotoxicity
p-cymene	134.22	0	0	0	4.100	-3.63	Inactive	Active	Inactive	Inactive
γ-terpinene	136.130	0	0	0	4.307	-3.985	Inactive	Inactive	Inactive	Inactive
Cuminaldehyde	148.090	1	0	17.070	2.887	-2.949	Inactive	Inactive	Inactive	Inactive
Apigenin-7-O-glucoside	432.110	10	6	170.050	1.239	-3.721	Inactive	Inactive	Inactive	Inactive
Fluconazole (positive control)	306.100	7	1	81.650	0.403	-1.729	Active	Inactive	Inactive	Inactive

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4. Discussion

Overgrowth of *C. albicans* in humans under suitable conditions led to various infections. secreted aspartic proteinase plays a key role in the pathogenicity of this microorganism by contributing to degrading host extracellular proteins. Therefore, the discovery of inhibitors of this enzyme as antifungal agents has attracted the attention of researchers [16]. Recently, the use of phytochemicals with medicinal applications has increased significantly due to the low side effects and high capacities but the mechanism of many of them is still unknown [17]. *C. cyminum* is one of these widely used plants that has many diverse bioactive substances for medicinal uses [18]. Hence, The current research aimed to analyze the potential of the main compounds of *C. cyminum* in inhibiting the active site of the secreted aspartyl proteinase of *C. albicans* compared to fluconazole.

Nowadays by the methods of in silico approaches, identification and discovery of new drugs speed up. With this technique, it is possible to place the three-dimensional structure of small ligands generated by the computer in a receptor structure and examine the orientations, interactions, and energy of complex in different positions for drugs or vaccine design [19-21]. In our research, molecular docking studies of in silico approaches were used to study the ligand-receptor interactions and binding affinities. Based on the docking results of the selected compounds, *p*-cymene, *γ*-terpinene, cuminaldehyde, and apigenin-7-O- glucoside had more than 50 % similarity with fluconazole in the interaction. The binding energy level was varied from -3.94 to -10.48. The binding energy parameter has been used to determine which ligand has a high affinity and stable complex with the protein. In this parameter, a more negative value indicates a high affinity. Apigenin-7-O- glucoside has the most negative affinity energy value and high binding similarity (80 %) with fluconazole as the positive control. Both of apigenin-7-O- glucoside and fluconazole have interaction with Thr221, Asp32, Asp218, Asp86, Gly34, Ile123, Tyr84, and Gly85 in active site.

The interactions observed in the studied compounds were consistent with the reports of other researchers. Meylani et al., to obtain antifungal compounds from the phytochemicals of *Cinnamomum zeylanicum*, performed the molecular docking process, which based on their reports, cinnamaldehyde, cyclopentane, pyrantel hydrochloride, eugenol, hexadecenoic acid, and pepstatin as a standard ligand interacts with Asp86, Ile123 in active site of secreted aspartyl proteinase, similar our studied compounds [22]. In our study, three aspartic acids, Asp32, Asp218, and Asp86 were observed in the interaction with both compounds of apigenin-7-O- glucoside and fluconazole. In the study of Meenambiga et al., secreted aspartyl proteinase (PDB ID: 2QZX) was targeted to extract inhibitors with antifungal activity. They showed that the best compound is emodin with binding energy −6.35. Emodin interacts with Asp32, Asp218, and Asp86. In addition, Thr221, Gly34, Ile123, Tyr84, and Gly85 also were reported as the amino acids involved in the interaction with this compound [23]. Binding with amino acids Asp32, Asp86, Ile123, and Ile30 was also reported in the molecular docking analysis of micafungin, which is known as a standard antifungal drug [24]. Furthermore, Yean Lum et al. synthesized ligands with a peptide structure to obtain compounds that inhibit secreted aspartyl proteinase (PDB ID: 2QZX). In this research, the interactions of newly synthesized

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compounds were obtained by using Autodock vina. Similar to our studied compounds, two key residues Asp32 and Asp86 have been reported as involved amino acids [25].

In addition to in silico studies, *C. cyminum* has also shown good antifungal effects in laboratory tests. Based on an in vitro study on the antifungal activity of several Iranian medicinal plants, The highest activity was observed for *C. cyminum* L. with a zone of inhibition of 27.4 ± 2.1 mm [26]. The antifungal activity of *C. cyminum* against panax notoginseng pathogens has also been proven by Huo et al [27].

Physicochemical properties are one of the most important parameters in the design and introduction of safe drugs with high performance. The Physicochemical properties of studied compounds revealed that all ligands have suitable pharmacokinetic properties. Molecular weight (MW) values for all 5 compounds are less than 500 Da and the topological polar surface area (TPSA) of all ligands except ligand 4 is in the range of 0–140 Å2. According to the Drug-Like Soft rule, for all ligands, the number of hydrogen bond acceptors (NHA) is 0-12 and the number of hydrogen bond donors (NHD) is 0-7. For a compound to be used as an oral drug, its LogP value should be less than 5, all compounds were within the range of oral drugs with a Log P < 5. The dissolution of the investigated compound is the first step in the absorption process of the drug, which is related to the logarithm of aqueous solubility value (logS). The optimal range is between -4 to 0.5 log mol/L and all ligands are in this range [28, 29].

This article gives useful information about the inhibitory effect of the main compounds of *C. cyminum* in targeting secreted aspartyl proteinase of *C. albicans*, However, further analysis such as molecular dynamics (MD) simulations and laboratory testing through in vitro and in vivo research are required to validate these results.

5. Conclusion

In this work, the structure of the main compounds of *C. cyminum* were retrieved from the ChemSpider database and HyperChem Professional software respectively, and then in silico molecular docking technique was performed to identify potential inhibitors against *C. albicans*, by targeting secreted aspartyl proteinase enzyme. Finally, physicochemical properties and toxicity predictions were obtained for each compound. The results of this research showed that binding energies for all compounds against the target enzyme ranging from -3.94 to -10.48 kcal/mol. among studied compounds, apigenin-7-O-glucoside has a greater negative binding affinity range with the active site of secreted aspartyl proteinase. Furthermore, 80 % Binding similarities with fluconazole and, suitable pharmacokinetic and safety profiles of this compound make it as a suggested potent inhibitor for conducting more clinical trials.

Author contributions

A.A. participated in designing the study. A.A. participated in generating the data for the study. A.A., N.G., and K.D. participated in gathering the data for the study. A.A. participated in the analysis of the data. A.A., N.G., and K.D. wrote the majority of the original draft of the paper. AA, N.G., and K.D. participated in writing the paper. AA, N.G., and K.D. have reviewed the pertinent raw data on which the results and conclusions of this study are based. AA, N.G., and K.D. have approved the final version of this paper. AA guarantees that all individuals who meet the Journal's

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authorship criteria are included as authors of this paper.

Conflicts of interest

The authors declare there is no conflict of interest.

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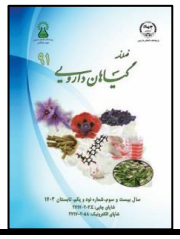

مقاله تحقیقاتی

پتانسیل ضدقارچی ترکیبات اصلی *Cuminum cyminum* L. در هدف قرار دادن آسپارتیل پروتئیناز ترشحی کاندیدا آلبیکنس در مقایسه با فلوکونازول

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اطلاعات مقاله

گل‌واژگان:

کاندیدا آلبیکنس

Cuminum cyminum L.

شبیه‌سازی مولکولی

اتصال سمیت

آسپارتیل پروتئیناز ترشحی

چکیده

مقدمه: کاندیدا آلبیکنس به طور طبیعی در فلور طبیعی انسان وجود دارد. این میکروارگانیسم به دلیل عدم تعادل در ترکیب میکروبیوم، به ویژه در شرایط سیستم ایمنی ضعیف، به یک قارچ فرصت طلب تبدیل می‌شود. تعداد کم ضدقارچ‌های در دسترس، سمیت شدید، عوارض جانبی، هزینه بالا و ظهور مقاومت دارویی از جمله محدودیت هایی است که پزشکان در تجویز داروهای ضدقارچ دارند. **هدف:** پژوهش حاضر با هدف بررسی پتانسیل ضد قارچی ترکیبات اصلی *Cuminum cyminum* L. در مهار آسپارتیل پروتئیناز ترشحی کاندیدا آلبیکنس در مقایسه با فلوکونازول انجام شد. **روش بررسی:** در این مطالعه از تکنیک‌های in silico استفاده شد. مواد بیوشیمیایی اصلی زیره سبز بدست آمد و بهینه شد. ساختارهای دو بعدی و سه بعدی ترکیبات شیمیایی به ترتیب از پایگاه داده ChemSpider و نرم‌افزار HyperChem بازیابی شدند. Auto Dock Vina و Discovery Studio 2024 Client برای شناسایی بازدارنده قوی برعلیه جایگاه فعال آنزیم انجام شد. در نهایت، خواص فیزیکوشیمیایی و سمیت مهارکننده‌ها به دست آمد. **نتایج:** نتایج Auto Dock Vina نشان داد که پتانسیل مهاری Apigenin-7-O-glucoside هشتاد درصد شباهت با فلوکونازول دارد و انرژی اتصال آزاد بالایی از خود نشان می‌دهد (ΔGbind: 10.48 kcal/mol)-سیزده باقی مانده آمینواسیدی در تعامل بین بهترین لیگاند و گیرنده Thr221، Asp32، Asp218، Asp86، Gly34، Ile123، Tyr84، Gly85، Ile30، Ser35، Ala119، Ile216، و Lys193 دخیل هستند. **نتیجه‌گیری:** مطالعه حاضر تایید کرد که Apigenin-7-O- glucoside موجود در *Cuminum cyminum* می‌تواند یک مهارکننده امیدوارکننده در برابر آسپارتیل پروتئیناز ترشحی باشد. با این حال، هنوز نیاز به تحقیقات بالینی آینده برای حمایت از این یافته‌ها وجود دارد.

مخفف‌ها: 2D، دو بعدی؛ 3D، سه بعدی؛ EC، شماره کمیسیون آنزیم؛ PDB، بانک اطلاعات پروتئین؛ MW، وزن مولکولی؛ TPSA، مساحت سطح قطبی توپولوژیکی؛ NHA، تعداد پذیرندگان پیوند هیدروژنی؛ NHD، تعداد دهندگان پیوند هیدروژنی

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