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# Examination of the anti-*Candida* activity of Vitexin against *Candida* species inducing fungal infection

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**Abstract**

Infections caused by *Candida* species have become a serious problem threatening global health systems today. This situation reveals the need to investigate new antifungal agents that can be alternatives to current treatment approaches, which are safer, more accessible and more effective. In this context, the potential anti-*Candida* effect of vitexin, a natural compound belonging to the flavonoid family, on different *Candida* species under *in vitro* conditions, and experimental methods, reveals the levels of its impact against different *Candida* species. In this study, vitexin's minimum inhibitory concentration (MIC) values against *Candida* species were determined using dilution methods. The activity of vitexin against *Candida glabrata* (ATCC 90030), *Candida parapsilosis* (ATCC 22019), *Candida tropicalis* (ATCC 13803), *Candida krusei* (ATCC 14243), and *Candida albicans* (ATCC 14053) taken from the American Type Culture Collection (ATCC) was measured. According to broth microdilution results, the MIC value of vitexin was determined as 12 mg/mL against *C. glabrata, C. tropicalis, and C. albicans*, and 24 mg/mL against *C. krusei and C. parapsilosis*. According to the results of the agar dilution method, the MIC value was found to be 24 mg/mL for all *Candida* species. When the results of agar dilution and broth microdilution methods were compared, slight differences were observed in the MIC values of vitexin against *Candida* species. The data obtained from the study indicate that vitexin may be evaluated as a potential agent for treating various *Candida* infections. Thus, it is thought that the anti-*Candida* effect of vitexin can form a scientific basis for more comprehensive preclinical and clinical studies to be conducted in the future.

**Keywords:** Anti-*Candida* effect, flavonoid, minimum inhibitory concentration (MIC), vitexin

## Introduction

Opportunistic fungal infections have increased in recent years and are primarily seen in hospital environments and individuals with weakened immune systems. However, it is known that *Candida* species cause the most common superficial and invasive infections [1]. There are more than 200 *Candida* species, and the most common cause of non-invasive skin and mucosal candidiasis is *Candida albicans*. However, the incidence of non-albicans *Candida* species such as *Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei, Candida lusitaniae, Candida dubliniensis* and *Candida guilliermondii*, which are the causative agents of candidiasis, has increased by more than 50% [2,3]. *Candida* infections, which are associated with high mortality rates, show resistance through multiple mechanisms, such as limited use of antifungal drugs and natural drug resistance of biofilms. This situation causes *Candida* species to become the third or fourth most common cause of hospital-acquired infections [4]. The prevalence of fungal infections has led to a continuous search for new drugs that have biocidal activity and no side effects. This poses a significant challenge because fungi are eukaryotic like humans, and many commercial drugs cause cytotoxicity in the liver and kidneys of the host as a result of the similarity between eukaryotic cells [1,5]. *C. albicans* continues to be the microorganism responsible for the majority of infections in HIV-positive and HIV-negative individuals [6]. In patients with candidiasis, the presence of a central venous catheter, antibiotic therapy, previous surgical interventions, especially gastrointestinal system surgery, TPN administration,

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colonization by *Candida* species, presence of neutropenia, use of steroids, and length of stay in the intensive care unit are known risk factors for candidiasis-related mortality [7]. Treatment of infections caused by *Candida* is arduous. Human infections affecting mucosal surfaces cause serious health problems, especially in developing countries in tropical and subtropical regions. Although there are available antimycotic drugs, there are several problems that limit the use of these drugs. These problems include low bioavailability, poor solubility properties, emergence of resistant microorganisms, and toxic effects of drugs. For these reasons, the need for new antimicrobial agents that are more effective, safer, and advantageous against resistance development is increasing [8]. Treatment of *Candida* infections takes a long time and creates a serious economic burden on health institutions. For all these reasons, discovering new antifungal agents that are natural, easy to use, and readily available is important.

Vitexin is an apigenin flavonoid with low water solubility from natural sources [9]. Buckwheat, mung bean, *Passiflora foetida* (passionflower), *Ficus deltoidea* (mistletoe fig) and *Pigeon pea* are good sources for obtaining vitexin. Buckwheat, which is statistically significant both in the dark and in the light and produces the highest sprout biomass, has the highest vitexin content [10,11]. Flavonoids are polyphenol-type compounds naturally found in plants and provide various health benefits. These substances act as antioxidants by protecting against free radicals that can cause cell damage in the body. At the same time, they support the immune system with their anti-inflammatory effects and may help prevent the development of some chronic diseases [12]. Studies have shown that various flavonoids, especially vitexin, exhibit various anti-inflammatory, antioxidant, antimicrobial, antiallergic, and neuroprotective effects [13-15]. In this study, the anti-*Candida* effect of vitexin was tested against various *Candida* strains, and the Minimum Inhibitory Concentration (MIC) values of vitexin were determined against each *Candida* strain.

## Material and Methods

### Vitexin and Chemical Reagents

Vitexin was supplied by BLDpharm (CAS No: 3681-93-4, Shanghai, China). This compound, whose molecular formula is $C_{21}H_{20}O_{10}$, is defined as 5,7-dihydroxy-2-(4-hydroxyphenyl)-8-β-D-glucopyranosyloxy-4H-1-benzopyran-4-one. Its molecular weight is 432.38 g/mol, and its purity is 98.37%. Its physical appearance is that of a light yellow crystalline powder, and its chemical structure is shown in Figure 1. Dimethylsulfoxide (DMSO) used as a solvent was supplied by Sigma-Aldrich (CAS No: 67-68-5, Darmstadt, Germany). Rezasurin sodium salt used to detect the growth of *Candida* strains was supplied by Sigma-Aldrich (CAS No: 62758-13-8, Darmstadt, Germany).

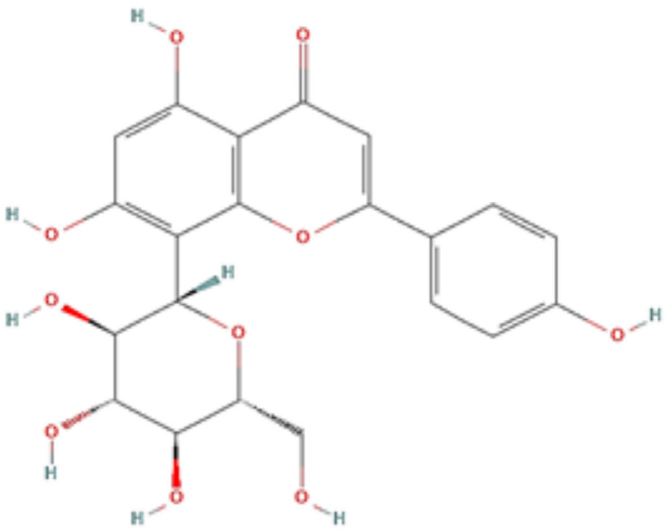

**Figure 1.** Chemical composition of vitexin [22].

### Anti-*Candida* Activity of Vitexin

### Broth Microdilution Method

In order to determine the anti-*Candida* activity of vitexin, the effects of various concentrations of vitexin on five different *Candida* species were investigated. *Candida* strains used in the study were *C. glabrata* (ATCC 90030), *C. parapsilosis* (ATCC 22019), *C. tropicalis* (ATCC 13803), *C. krusei* (ATCC 14243) and *C. albicans* (ATCC 14053). Sabouraud agar medium was used for the growth and maintenance of cultures of these species. To determine the minimum inhibitory concentration (MIC), 48 mg of vitexin was dissolved in 250 µL of DMSO. In the 96-well microplates used in experimental analyses, 150 µL of Sabouraud Broth (SB) medium was added to the first well and 100 µL to the other wells. Then, 50 µL of DMSO solution containing 9.6 mg of vitexin was added to the first well, and this process was performed by doing serial two-fold dilutions. The final concentrations of vitexin were gradually diluted between 48 mg/mL and 0.094 mg/mL. Suspensions containing *Candida* strains were prepared according to the 0.5 McFarland standard and brought to a density of approximately $1\text{-}1.5\times10^6$ CFU/mL. The prepared suspension was inoculated into each experimental well (except for the negative control) at a rate of 1 µL. As a negative control, the eleventh well was arranged to contain only SB, and this well was used as a reference to monitor whether there was contamination. The positive control group contained only *Candida* strains and SB in the twelfth well, and this group was used to confirm the viability of *Candida* strains.

The microplate was incubated at 36.5 °C for 24 hours. After incubation, a resazurin solution was added to all wells to

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evaluate metabolic activity quantitatively. Resazurin is a compound with high redox sensitivity that interacts with the metabolism of living cells and transforms from blue to pink resorufin. This feature is an important tool in the evaluation of metabolic activity of living cells. In the final stage, color changes in the microplates were evaluated visually, and MIC values were determined. This method effectively demonstrates the antifungal effect of vitexin and allows for a comparison of its activity with different *Candida* strains. The MIC values obtained reflect vitexin's inhibitory potential and effectiveness against each *Candida* strain.

### Agar Dilution Method

In the study carried out using the agar dilution method, 144 mg of vitexin was dissolved in 720 µL of DMSO. This prepared solution was added to 12 mL of Sabouraud agar medium to obtain a homogeneous mixture. Then, this mixture was diluted with a sequential two-fold dilution technique, and thus, an agar medium containing vitexin was prepared with an initial concentration of 48 mg/mL. With this process, agar plates with different vitexin concentrations were obtained. The prepared agar plates were divided into five separate areas in order to inoculate each of the *Candida* strains.

*Candida* strains were suspended in distilled water before being used in the experimental environment, and the 0.5 McFarland standard was meticulously adjusted to ensure their accurate densities. 1 µL suspension of each *Candida* strain was taken and inoculated into the designated sections of agar plates containing different concentrations of vitexin. During incubation, *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis* and *C. albicans* species were added from the first zone to the fifth zone on each plate, respectively. All plates were incubated at 36.5 °C for 24 hours to observe fungal growth. During this incubation period, the effects of different vitexin concentrations on the growth of *Candida* strains were carefully monitored, and fungal growth in each zone was recorded. The study was designed in detail to evaluate the antifungal effect of vitexin and to compare the potential inhibition levels on different *Candida* strains. Thus, important data were obtained on how vitexin-containing media affect the growth of *Candida* strains.

## Results

### Results of Anti-*Candida* Activity Tests

### Results of Broth Microdilution Method

The findings of the Broth microdilution test are given in Figure 2. In this method, the change of color in the wells from blue-purple to pink indicates that live microorganisms metabolize resazurin and convert it to resorufin, indicating that microbial growth has occurred [17].

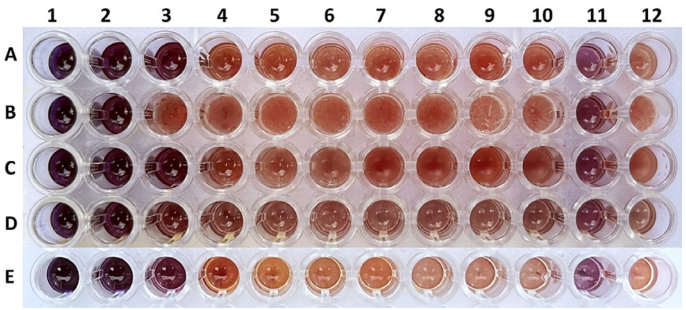


**Figure 2.** Result of antifungal activity test against *C. glabrata* (A), *C. krusei* (B), *C. tropicalis* (C), *C. parapsilosis* (D), *C. albicans* (E) using the broth microdilution method.

The concentrations in the 1st to 10th wells are 48, 24, 12, 6, 3, 1.5, 0.75, 0.375, 0.188, 0.094 mg/mL, respectively. The 11th and 12th wells are negative and positive control groups. As a result of the microdilution method, it was observed that *C. glabrata*, *C. tropicalis*, and *C. albicans* grew starting from the fourth well. Based on these findings, the MIC value of vitexin was determined as 12 mg/mL for three *Candida* species. *C. krusei* and *C. parapsilosis* showed growth starting from the third well. According to these results, the MIC value of vitexin for *C. krusei* and *C. parapsilosis* was determined as 24 mg/mL. These data are consistent with the results obtained by the agar dilution method (Table 1). In addition, the 11th well of the microplate was evaluated as a negative control, confirming that there was no contamination during the application period, while the 12th well was used as a positive control, showing the viability of the tested microorganism.

**Table 1.** MIC values of vitexin against different *Candida* species obtained using the broth microdilution method

| Microorganisms | Minimum Inhibitory Concentrations (MICs) (mg/mL) |
|---|---|
| ***C. glabrata*** | 12 |
| ***C. krusei*** | 24 |
| ***C. tropicalis*** | 12 |
| ***C. parapsilosis*** | 24 |
| ***C. albicans*** | 12 |

### Agar Dilution Method Results

After overnight incubation, all agar plates and microplates were evaluated in detail to determine MIC values. MIC values were calculated according to the criteria determined by the Clinical and Laboratory Standards Institute (CLSI) [18].

In the tests performed with the agar dilution method, it was observed that all 5 *Candida* strains grew in all plates except plate 1 in plates containing 0.5 mg/mL vitexin. Anti-*Candida* activity test results were determined as 24, 12, 6, 3, 1.5, 0.75, 0.375, 0.188, 0.094, 0.047, 0.023 mg/mL in plates 1 to 11, respectively. Plate 12 was used as a positive control to verify the viability and purity of all *Candida* strains tested (Figure 3, Table 2).

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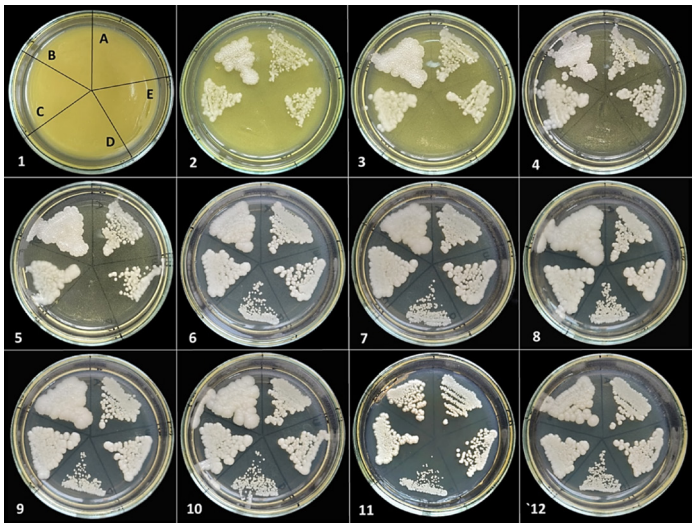


**Figure 3.** Result of antifungal activity test against *C. glabrata* (A), *C. krusei* (B), *C. tropicalis* (C), *C. parapsilosis* (D), *C. albicans* (E) using the agar dilution method

**Table 2.** MIC values of vitexin against different *Candida* species were obtained using the agar microdilution method

| Microorganisms | Minimum Inhibitory Concentrations (MICs) (mg/mL) |
|---|---|
| ***C. glabrata*** | 24 |
| ***C. krusei*** | 24 |
| ***C. tropicalis*** | 24 |
| ***C. parapsilosis*** | 24 |
| ***C. albicans*** | 24 |

## Discussion

In many ancient societies, plants have various biological effects that provide the scientific basis for traditional medicine [19]. These plants have been identified as antibiotic, antifungal, and antiviral agents and, therefore, can show protective effects against various pathogens [20]. In urinary tract infections (UTI), one of the most common fungal infections, *C. albicans*, *C. glabrata* and *C. tropicalis* species are considered the most common sources of infection [21]. This study observed that vitexin was similarly effective on different *Candida* species, and this effect became more pronounced, especially under high-temperature conditions. It should also be considered that environmental factors such as temperature, as well as other parameters such as solubility and pH level, can affect this effectiveness. Resistance to common anti-*Candida* treatments is an important problem reported by medical organizations and clinical studies today [22]. These findings further encourage the research of alternative treatment options, such as natural plant extracts.

In this study, the antifungal activity of vitexin against different *Candida* species was evaluated using two different in vitro methods: Agar dilution and Broth microdilution techniques. The findings revealed that vitexin showed significant antifungal activity, especially against *Candida* species, which are common and tend to develop resistance to treatment. This suggests that vitexin may be a naturally derived treatment agent that can be considered an alternative to existing antifungal drugs. In this context, investigating molecules of natural origin, especially compounds of plant origin represents an important scientific approach to developing alternative and complementary treatment approaches.

The study data revealed that the anti-*Candida* effect of vitexin may vary depending on the applied method and experimental conditions. In particular, vitexin was applied at 55°C in the agar dilution method, while broth microdilution was applied at room temperature (20–25°C). This temperature difference is a possible reason for the slight differences observed in MIC values. The data obtained with the broth microdilution method showed that the MIC value was 12 mg/mL for *C. glabrata*, *C. tropicalis*, and *C. albicans* species and that these species were more sensitive to vitexin. On the other hand, this value was determined as 24 mg/mL for *C. krusei* and *C. parapsilosis* species. On the other hand, the MIC value measured as 24 mg/mL for all *Candida* species in the agar dilution method suggests that the antifungal effect of vitexin is more homogeneous among species under high-temperature conditions. It is thought that the temperature difference in the dilution methods may play a role in the effectiveness of vitexin and, thus, may have caused differences in MIC values. High temperature in the agar dilution method may have increased the effectiveness of vitexin and generally led to higher MIC values [23]. Decades of research have shown the existence of a wide range of biological activities of vitexin. These include cancer, cognitive deficits, depressants, analgesia, cardiac hypertrophy, hypertension, diet, obesity, infections, and metabolic disorders [24]. Moreover, vitexin can donate electrons and thus acts as a good radical scavenger [25]. A study proves that vitexin can effectively eliminate excess oxygen free radicals by increasing antioxidant enzyme activities, protect lipids, proteins and DNA from oxidative damage, and reduce or stop the damage of cells and tissues, thus maintaining the normal functions of cells and tissues and delaying the aging process induced by D-galactose [26].

It is known that vitexin reduces NO (nitric oxide) production by neutrophils [27]. Activated isolated human peripheral blood neutrophils show a significant increase in the production of nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and myeloperoxidase (MPO). However, incubating neutrophils with natural flavonoid compounds such as quercetin or vitexin before activation significantly reduces the production of these proinflammatory mediators [28]. This finding suggests that both compounds can potentially suppress the inflammatory response and may have regulatory effects on neutrophil activity. In some studies, vitexin has been shown to inhibit the production of proinflammatory cytokines such as IL-1β, IL-6, and IL-33 in mouse models. These findings suggest that natural

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compounds with flavonoid structures, such as vitexin, may regulate the inflammatory response effectively. They thus may be considered potential therapeutic agents in the prevention and treatment of various inflammatory diseases [29]. In addition, studies have shown that vitexin is beneficial in alleviating diseases by regulating the composition of the intestinal flora and can significantly inhibit the progression of colitis-associated carcinogenesis by regulating macrophage polarization [30].

Vitexin increases cell survival in neonatal rat cardiomyocytes cultured before anoxia and reoxygenation, decreases creatine kinase (CK) and lactate dehydrogenase (LDH) levels, ischemia-related indicators, and reduces apoptotic cells and intranarcotic $Ca^{2+}$ overload [31]. In rats treated with Lagenaria siceraria (molina, cucurbitaceae) powder containing vitexin in methanol extract and L-arginine, no necrosis or inflammation of the heart was observed, while a significant decrease in serum cholesterol was detected, indicating the presence of cardioprotective activity [32]. In addition, a study that reduced the frequency of cough in mice exposed to citric acid confirmed the pharmacological potential of vitexin on respiratory tract disease and also showed an expectorant and antitussive effect for the complex at low doses [33].

Although repeated application before surgery does not have a preventive effect on postoperative pain, the positive findings regarding the antinociceptive effects produced by acute or repeated vitexin treatment suggest that vitexin may be helpful as a new alternative agent for treating postoperative pain. More importantly, the antinociceptive effects of vitexin can be reversed by pretreatment with naltrexone or bicuculline, suggesting that both opioid receptors and GABA-A receptors contribute to the antinociception of vitexin in postoperative pain [34]. Vitexin and its derivatives are being investigated for their blood glucose-regulating effects. Studies in rodent models have reported that orally administered vitexin or isovitexin provides a significant dose-related decrease in postprandial blood glucose levels [11,35]. In particular, isovitexin has been found to have a significant blood glucose-lowering effect and suppress glucose elevation in healthy and diabetic rats [36].

Vitexin is a class of polyphenolic flavone secondary metabolites widely distributed in all higher plants. In plants, polyphenolic secondary metabolites play a defensive role against various microbial pathogens [37]. In the experiment conducted on Tamarindus indica leaves, whose phytochemical composition is orientin and vitexin, the antimicrobial activities of leaf extracts showed the significant activity against the test organisms (*Micrococcus luteus, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). The ethanol extracts in this study may have higher solubility for more phytoconstituents, thus having the highest antibacterial activity [38]. The attachment of *S. aureus* to the surface of animal cells is an important step in the infection process [39]. Hydrophobic interactions are thought to cause bacteria to adhere to host tissues [40]. The role of vitexin in reducing the surface hydrophobicity of *S. aureus* is being investigated; studies have shown that vitexin reorganizes the morphology of host tissue in cases of S. aureus biofilm infection and related pathogenesis and also provides protective immune function [41].

In the study examining the antimicrobial and antibiofilm activities of vitexin against *P. aeruginosa*, each of vitexin, azithromycin and gentamicin showed antimicrobial activity against *P. aeruginosa*. However, the effect of vitexin was found to be lower. Vitexin has a limited effect compared to azithromycin and gentamicin and shows only a moderate effect. However, combining vitexin and antibiotics, especially gentamicin, significantly inhibits biofilm formation and shows a synergistic effect. The combination of gentamicin and vitexin increases the reduction of biofilm by 83.44% [42]. Vitexin can weaken the biofilm formation of *P. aeruginosa* in combination with antibiotics, while its effect alone is limited.

*In vitro* studies conducted to evaluate the antiviral effects of vitexin-rich extracts obtained from the fruits and leaves of the *Vitex polygama* (Verbenaceae) plant have shown that these extracts have an antiviral dose-dependent impact on acyclovir-resistant *Herpes simplex* virus type 1. In particular, a fraction of the leaf extract has been found to inhibit viral receptors in HEp-2 cells, preventing the entry and spread of the virus into the cell. These findings suggest that *V. polygama* extracts may be potential therapeutic agents against resistant viral infections [43].

In studies conducted to test vitexin for antifungal activities against phytopathogenic fungi of agricultural importance, such as *Botrytis cinerea, Rhizoctonia solani, Sclerotinia sclerotiorum,* and *Fusarium solani*, it has been determined that all of these compounds inhibit fungal growth at certain levels. However, vitexin has significant antifungal activity [43]. Previous molecular analyses have shown that vitexin exhibits potent and specific binding to the active site of the sterol 14-α-demethylase enzyme found in *C. albicans*. This binding constitutes the basic mechanism of the antifungal effect of vitexin, and it has also been shown that this compound forms a stable complex with the SAP5 protease enzyme [44]. SAP enzymes are involved in various biological functions such as the formation of hyphal structure, cell adhesion to surfaces and the change of phenotypic characteristics of the microorganism [45]. These enzymes contribute to different aspects of pathogenicity by means such as the degradation of proteins, regulation of gene expression, formation of immune system responses, and development of resistance to enzyme inhibitors, and therefore stand out as an important virulence factor [46].

In this study, according to the dilution results, the MIC values of vitexin against *Candida* species varied between 12 mg/mL and 24 mg/mL, indicating that vitexin showed similar anti-*Candida* activity on all species under different temperatures. This suggests that the efficacy of vitexin on *Candida* species

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may vary depending on the temperature and the methodology used. These findings indicate that the efficacy of vitexin against *Candida* species may be an important alternative, even for some treatment-resistant strains. In particular, it is reported by the Centers for Disease Control and Prevention (CDC) that more than 7% of all *Candida* infections caused by *C. albicans*, *C. parapsilosis*, *C. auris*, and *C. glabrata* are resistant to fluconazole [47]. This makes it essential to investigate other potential anti-*Candida* treatments, such as natural plant extracts. In addition, this study on the antifungal activity of vitexin has been limited to in vitro conditions only. Future preclinical and clinical studies can evaluate whether this compound is an effective therapeutic agent from a broader perspective. In particular, these findings, which suggest that vitexin can be used as a potential alternative in treating *Candida* infections, provide an important basis for future research. However, more extensive studies are needed on the efficacy and safety of vitexin in clinical use. The development of resistance to antifungal treatments by *Candida* species is a process that occurs through genetic variations and mutations. How vitexin affects these resistance mechanisms can be observed more clearly in studies conducted with resistant strains. In addition, it should be considered that the genetic and phenotypic characteristics of different *Candida* species can affect the response to treatment and thus lead to different results during the treatment process. In the next step, multicenter clinical studies and large-scale preclinical tests are needed to determine whether vitexin is an effective treatment tool. Such studies will be an important step in determining vitexin's role in treating *Candida* infections.

## Conclusion

This study demonstrates that vitexin has a significant antifungal potential against *Candida* species and emphasizes that this effect may vary depending on the experimental conditions. Evaluating vitexin as an alternative or complementary treatment to conventional antifungal agents will only be possible with comprehensive preclinical and clinical studies. Advanced studies to be conducted in this direction are important in detailing the mechanisms of action and evaluating the suitability of this compound for therapeutic use. In conclusion, the obtained data support the anti-*Candida* activity of vitexin and indicate that this compound may have a potential place in future antifungal treatment strategies.

These results show that the mechanisms of action of vitexin may not be limited to direct antifungal activity, and environmental conditions (e.g., temperature, pH, solubility) may play a decisive role in this activity. To better understand the pharmacological profile of vitexin, studies examining such parameters in detail are needed. In particular, investigating potential biochemical pathways such as binding to the cell membrane, inhibiting cell wall synthesis, and causing cellular stress through producing reactive oxygen species (ROS) is important in clarifying the compound's mechanism of action. In addition, the antifungal effect of the vitexin compound should be tested not only in laboratory conditions but also on living organisms. In this context, in addition to animal model studies, determining pharmacokinetic and pharmacodynamic parameters will provide information on critical issues such as how the drug is distributed, metabolized, and excreted in the body. In addition, evaluation of possible toxicological effects is necessary for the usability of vitexin as a safe pharmaceutical agent. Following preclinical studies, verifying efficacy with prospective, randomized, double-blind clinical studies is a critical step for vitexin to find a place in modern medicine.

**Conflict of Interests**

*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**

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**Ethical Approval**

*No ethical approval is required for the study.*

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