



## REVIEW: A Review of Antifungal Activities of *Ziziphora clinopodioides*

Mohammad Eghbali

Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran.

Amirhosein Arab  
Mohammad Hossein  
Hosseinzadeh

Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.  
Student Research Committee, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.  
Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran.

Fatemeh Bodaghabadi  
Mohammad Ali  
Ebrahimzadeh

Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran.

### ARTICLE INFO

**Submitted:** 03 Feb 2022

**Accepted:** 01 May 2022

**Published:** 04 Sep 2022

### Keywords:

Antifungal Agents;

*Candida albicans*;

*Candida glabrata*;

Mountain Mint;

*Ziziphora clinopodioides*

### Correspondence:

Mohammad Ali Ebrahimzadeh,  
Pharmaceutical Sciences Research  
Center, Faculty of Pharmacy,  
Mazandaran University of  
Medical Science, Sari, Iran.

**Email:** zadeh20@gmail.com

**ORCID:** 0000-0002-8769-9912

### Citation:

Eghbali M, Arab A, Hosseinzadeh  
MH, Bodaghabadi F,  
Ebrahimzadeh MA. A Review of  
Antifungal Activities of *Ziziphora  
clinopodioides*. Tabari Biomed  
Stu Res J. 2022;4(3):16-27.

10.18502/tbsrj.v4i3.10514

### ABSTRACT

*Ziziphora clinopodioides*, also known with vernacular names such as Kakuti-e kuhi, Pinah kuhi, Ankh, Lip vanilla, and mountain mint, is a wild flowering plant that belongs to the Lamiaceae family. It is used in treating typhoid fever, stomach strengthening, abdominal pains, inflammatory and cardiovascular disease, asthma, cough, bronchitis, insomnia, colds, flu, and other infectious diseases in traditional medicine. Additionally, *Z. clinopodioides* has various biological activities, including antibacterial, antimicrobial, anti-inflammatory, antioxidant, appetizer, carminative, antiseptic, and wound-healing properties. In this study, the antifungal activities of *Z. clinopodioides* were summarized. The Keywords were searched in Scopus until 19 October 2021 and the articles that contain relevant information about the antifungal activity of *Z. clinopodioides* were included. *Z. clinopodioides* leaf and aerial parts had significant antifungal activity against *Aspergillus flavus*, *Aspergillus parasiticus*, *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Trichophyton schoenleinii*. In some studies, its effects were higher than standards (such as amphotericin B, fluconazole, nystatin, and terbinafine). Therefore, it seems that *Z. clinopodioides* can be a good choice for more experimental and clinical studies as an antifungal agent.

## Introduction

*Ziziphora clinopodioides*, also known with vernacular names such as Kakuti-e kuhi, Pinah kuhi, Ankh, Lip vanilla, and mountain mint, is a wild flowering plant that belongs to the Lamiaceae family (1). *Z. clinopodioides* is globally distributed from the eastern Balkans, Southwest Asia, and central Asia to the Himalayas. The geographical distribution of this plant in Iran

is very diverse but mainly distributed in the foothills and high mountain heights. In traditional medicine, the complete decoction of *Z. clinopodioides* is used in treating typhoid fever, and its juice is used as a tonic after recovering from fever. Also, it has been used for treating stomach strengthening, abdominal pains (2), inflammatory and cardiovascular disease, asthma, cough,

bronchitis, insomnia, colds, flu, and other infectious diseases. *Z. clinopodioides* contains flavonoids, terpenoids, and alkaloids. Its flavonoids cause antioxidant properties by preventing lipid peroxidation (1). Additionally, *Z. clinopodioides* has various biological activities, including antibacterial, antimicrobial, anti-inflammatory, antioxidant (3) appetizer, carminative, antiseptic, and wound-healing properties (4, 5). *Z. clinopodioides* leaves, flowers, and stems are commonly used as wild vegetables or flavoring agents in food in indigenous areas (6). This study summarized the effects of *Z. clinopodioides* extracts and essential oils on pathogenic fungi. The Keywords included *Ziziphora clinopodioides*, fungi, antifungal agents, and its MeSh terms were searched in Scopus until 19 October 2021. The articles that contain relevant information about the antifungal activity of *Z. clinopodioides* were included.

## Results

### *Candida* spp.

*Candida* spp. are unicellular yeasts that have particular importance for human health. They are naturally present in the normal flora, mainly found on the skin, mucosal surfaces of the mouth, urogenital and gastrointestinal tracts, and vaginal mucosa (7). *Candida* spp. can cause a wide range of infections on mucosal surfaces under certain conditions. If this condition is not controlled, *Candida* spp. may pass through the epithelial barriers into the bloodstream (known as candidemia) and causes systemic and invasive infections (8) that practically can infect any organ. As a result, *Candida* spp. become the fourth leading cause of blood-borne infection in the USA. Adults have a risk of mortality between 14.5% to 49% when they contract these invasive disorders (9).

#### • *Candida albicans*

*Candida albicans* are the most common fungal infection in humans (over 90% of fungal infection cases and 50-60% of all invasive candidiasis cases). Deep mycoses

and vulvovaginal candidiasis are the most common *C. albicans* infection (70 to 90% of cases are vulvovaginal candidiasis) (10). Also, it is one of the most common causes of fungal infections in immunocompromised patients such as HIV-positive and cancer patients. *C. albicans* may be a commensal organism in normal people's oropharynx, gastrointestinal tract, and vaginal microbiota. However, it can become pathogenic if the usual flora balance is interrupted or the immune system is impaired. In immunocompromised patients, *C. albicans* can cause oropharyngeal, esophageal, or vulvovaginal candidiasis. Also, It can penetrate through the gastrointestinal mucosa to the bloodstream and cause hematogenously disseminated candidiasis in susceptible hosts (11).

#### • *Candida glabrata*

*Candida glabrata* is a significant pathogen in mucosal and bloodstream infections (15% of all candidemia cases). Its prevalence has increased significantly over the previous decade, and it is now the second or third most often isolated *Candida* species from all reported candidiasis cases. This yeast is of concern because of its decreased resistance to antifungal agents such as azoles that can cause substantial morbidity and mortality in the future and make it a critical problem. However, *C. glabrata* is deficient in some virulence factors, including hyphal development and release proteases ability (12, 13). The prevalence of *C. glabrata* is higher in adults than children but lower than neonates (14, 15). *C. glabrata* can colonize in the mouth, esophagus, intestines, and vaginal mucosal surfaces. Although information about its interaction with the host immune system is limited, it seems that the host immune system controls and inhibits the *C. glabrata* harmful features and prevents infection (16, 17).

#### • *Candida krusei*

*Candida krusei* is a diploid, dimorphic ascomycetous yeast that lives on healthy people's mucosal surfaces and causes 1.5 to 8% of candidiasis and candidemia cases

worldwide. It can induce life-threatening infections in immunocompromised people, such as patients suffering from hematologic malignancies or patients that are continuously used than azoles (18). *C. krusei* is correlated with superficial and systemic infections and can cause bronchopneumonia, vulvovaginal candidiasis (19), endophthalmitis, onycholysis, endocarditis, and osteomyelitis (18). Due to its innate resistance and decreased susceptibility to azoles and polyenes, this species is already a challenge. However, echinocandins are a promising approach for treating invasive *C. krusei* infection (20).

#### • *Candida guilliermondii*

*Candida guilliermondii* is an opportunistic pathogen that is widespread in the natural environment, human skin, and mucosal microflora and causes 1% to 3% of candidemia cases (21). It is the fourth cause of candidemia in Latin America (22, 23). This species has a lower virulence than other *Candida* species. *C. guilliermondii* causes invasive infections in immunocompromised patients (24), patients with hematologic malignancies (22), and patients that have intravascular devices (25, 26). Also, it can be colonized in skin, nails, blood, urine, genital tract, and soft tissue (27).

#### *Microsporum canis*

*Microsporum canis* is a zoophilic dermatophyte that causes dermatophytosis in animals and humans (28, 29). *M. canis* infection has been correlated to multifocal alopecia, scaling, and circular lesions in animals and localized forms of *Tinea capitis*, *Tinea corporis*, *Tinea pedis*, and onychomycosis in humans (30, 31). Females are more frequently infected than males in human patients older than 16 years. Direct contact with infected animals (especially dogs and cats) is the most common infection route in people. Although, the human-to-human infection has been documented regularly (30). A wide range of antifungal agents in oral and topical dosage forms are available. Griseofulvin, terbinafine, itraconazole, and fluconazole are used to treat severe infections

in animals and humans (32).

#### *Microsporum gypseum*

*Microsporum gypseum* is a geophilic fungus found in soil. Also, it is colonizing in keratinous substrates like nails, feathers, and hair. It is mechanically transmitted to humans from soil, fur-bearing animals (such as rodents, cats, and dogs) exposed to spores, and other humans (human-human infections are rare). It can cause dermatophytosis on rare occasions (33-35). Infection to *M. gypseum* depends on the patient's immune condition and the frequency of contact with the infectious source (36). The infection is common in youngsters and rural workers or under warm and humid conditions (37). *Tinea corporis* was the most common infection caused by *M. gypseum*, although it caused *Tinea kerion*, *Tinea capitis*, and *Tinea barbae* (33).

#### *Trichophyton rubrum*

*Trichophyton rubrum* is a phylum Ascomycota dermatophyte that is frequently identified in cases of *Tinea* and is the causal agent of superficial mycoses. It obtains nutrients from human skin protein and frequently causes infections of the skin, nails, hair follicles, dermis, subcutaneous tissue, and onychomycosis followed by *Tinea corporis*, *Tinea cruris*, *Tinea manuum*, and *Tinea pedis*. Although, the severe infection induced by *T. rubrum* is infrequent and usually occurs only in severely immunocompromised patients (38). The infection causes various lesions, including nodules, verrucous hyperplasia, granuloma, subcutaneous abscess, fistula, and folliculitis. Only a small percentage of critical patients will suffer lymphadenitis and widespread infection (39). *T. rubrum* infections are typically spread by contaminated clothing, towels, and linens. The treatment depends on the type and severity of the infection (40).

#### *Trichophyton mentagrophytes*

*Trichophyton mentagrophytes* are zoophilic dermatophytes that affect humans via animals' direct or indirect transmission. This

species has been associated with the infection of pets (hamsters, guinea pigs, chinchillas, and rabbits) and fur animals (ferrets, foxes, mink, and wolf). *T. mentagrophytes* infections are widespread in 3–7 years old youngsters and the elderly due to the care of pets that are asymptomatic carriers of the disease (41, 42). *T. mentagrophytes* strains resistant to antifungal drugs have been identified in various locations in Asia and Europe. India is the most affected country, with an estimated 11.4% risk of microbiological resistance to terbinafine (43).

### ***Trichophyton schoenleinii***

*Trichophyton schoenleinii* is an anthropophilic dermatophyte initially identified from various particular habitats throughout Eurasia and Africa. Fungus is disseminated with human contacts. *T. schoenleinii* is the causal agent of *Tinea favosa* of the scalp, an infection characterized by the formation of yellowish, cup-shape crusts or hyphae mats on the scalp (44, 45).

### ***Aspergillus flavus***

*Aspergillus flavus* is a plant pathogen and the second most frequent opportunistic pathogen in humans that generates severe superficial and invasive infections (4). *A. flavus* is the cause of fungal contamination of foods such as maize and nuts that produce aflatoxin B1 (a toxic secondary metabolite and a strong hepatocarcinogen) (46). The fungus is primarily related to infections of the respiratory system, brain, sinuses, eyes, and skin (with a higher prevalence in hot-arid locations) (47). It is correlated with an increased mortality rate in the absence of effective treatments, especially in immunocompromised patients (48). In immunocompromised patients, *A. flavus* causes various disorders such as keratitis, otitis, onychomycosis, and invasive sinonasal infection (49).

### ***Aspergillus parasiticus***

*Aspergillus parasiticus* is a saprophytic fungus that lives in soil and rotting plant matter. It is one of the *Aspergillus* species that

can produce aflatoxin and is highly aflatoxigenic (50). *A. parasiticus* creates aflatoxins B1, B2, G1, and G2. Aflatoxins are one of the most potent known carcinogens that are highly hepatotoxic and immunosuppressive (51). *A. parasiticus* grows on various sensitive food and feed crops such as maize, peanuts, rice, cotton seeds, and milk and produces aflatoxins that cause food contamination (52).

### ***Epidermophyton floccosum***

*Epidermophyton floccosum* is a dermatophyte found globally but more prevalent in tropical and subtropical climates such as Iran and Africa (53, 54). It is more pathogenic than most dermatophytes and attacks the skin (glabrous skin) and nails (54, 55), which causes superficial fungal infections such as *Tinea cruris*, *T. corporis*, *T. pedis*, *T. unguium*, and onychomycosis. *E. floccosum* can cause severe infections in immunocompromised patients (56) and is the most common cause of ringworm in human groins (53).

### **Antifungal activities of *Z. clinopodioides***

Antifungal activities of *Z. clinopodioides* were summarized in **Table 1**. Silver, magnesium, zinc, and titanium nanoparticles of aqueous extract of *Z. clinopodioides* leaf inhibited the growth of *C. albicans*, *C. glabrata*, *C. krusei*, and *C. guilliermondii* significantly in different studies (5, 57–59). In Ahmeda *et al.* study, silver nanoparticles of aqueous extract of *Z. clinopodioides* leaf (AgNPs@*Ziziphora*) were inhibited the growth of *C. albicans*, *C. krusei*, and *C. guilliermondii* better than fluconazole, amphotericin B, and nystatin. Also, AgNPs@*Ziziphora* inhibited the growth of *C. glabrata* better than nystatin (5). Magnesium nanoparticles of aqueous extract of *Z. clinopodioides* leaf (MnNPs@*Ziziphora*) were inhibited the growth of *C. albicans*, *C. krusei*, *C. glabrata*, and *C. guilliermondii* similar or better than fluconazole, amphotericin B, and nystatin (57). Zinc nanoparticles of aqueous extract of *Z. clinopodioides* leaf (ZnNPs@*Ziziphora*)





**Table 1: Antifungal activities of *Z. clinopodioides*.**

Part of plant	Type of extract	Dilution	Fungus	MIC (mg/ml)	MFC (mg/ml)	Disk diffusion test (mm)	Positive Control	reference
Leaves	Aqueous extract	AgNPs@Ziziphora (64 mg/ml)	<i>C. albicans</i>	4 ± 0	4 ± 0	40 ± 1	Efficacy of drugs on <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. krusei</i> , and <i>C. guilliermondii</i> in Disk diffusion: - Fluconazole (60 mg/ml): 38.6 ± 1.14, 44 ± 1.22, 42.2 ± 0.44, and 43 ± 0.7 mm, respectively	(5)
			<i>C. glabrata</i>	4 ± 0	4 ± 0	40 ± 1		
			<i>C. krusei</i>	2 ± 0	2 ± 0	43 ± 1		
			<i>C. guilliermondii</i>	2 ± 0	4 ± 0	44.2 ± 0.83		
		<i>Z. clinopodioides</i> (64 mg/ml)	<i>C. albicans</i>	8 ± 0	8 ± 0	34 ± 1.22	- Amphotericin B (60 mg/ml): 36 ± 1.22, 42.8 ± 1.09, 40 ± 0.7, and 41.2 ± 0.83 mm, respectively	(5)
			<i>C. glabrata</i>	8 ± 0	8 ± 0	35.6 ± 1.14		
			<i>C. krusei</i>	4 ± 0	8 ± 0	36.4 ± 0.89		
			<i>C. guilliermondii</i>	4 ± 0	8 ± 0	36.8 ± 1.09		
		AgNO <sub>3</sub> (64 mg/ml)	<i>C. albicans</i>	16 ± 0	32 ± 0	23.4 ± 0.89	- Nystatin (60 mg/ml): 35.2 ± 0.83, 39.6 ± 1.14, 39 ± 1.22, and 41 ± 0.7 mm, respectively	(5)
			<i>C. glabrata</i>	16 ± 0	16 ± 0	22 ± 0.7		
			<i>C. krusei</i>	8 ± 0	16 ± 0	26 ± 0.7		
			<i>C. guilliermondii</i>	8 ± 0	16 ± 0	25.6 ± 0.89		
		MnNPs@Ziziphora (64 mg/ml)	<i>C. albicans</i>	4 ± 0	4 ± 0	38.4 ± 0.89	Efficacy of drugs on <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. krusei</i> , and <i>C. guilliermondii</i> in Disk diffusion: - Fluconazole (60 mg/ml): 37.2 ± 0.83, 39.6 ± 0.89, 41.2 ± 1.3, and 42.2 ± 1.3mm, respectively	(57)
			<i>C. glabrata</i>	2 ± 0	4 ± 0	41.2 ± 1.3		
			<i>C. krusei</i>	1 ± 0	2 ± 0	44.4 ± 1.34		
			<i>C. guilliermondii</i>	2 ± 0	4 ± 0	42.2 ± 1.3		
		<i>Z. clinopodioides</i> (64 mg/ml)	<i>C. albicans</i>	4 ± 0	8 ± 0	29.4 ± 1.34	- Amphotericin B (60 mg/ml): 36.2 ± 1.3, 41.6 ± 0.89, 38.4 ± 1.34, and 42.4 ± 0.89 mm, respectively	(57)
			<i>C. glabrata</i>	4 ± 0	4 ± 0	29.8 ± 1.09		
			<i>C. krusei</i>	2 ± 0	2 ± 0	31 ± 1.22		
			<i>C. guilliermondii</i>	4 ± 0	4 ± 0	32.8 ± 0.44		
		MnSO <sub>4</sub> (64 mg/ml)	<i>C. albicans</i>	16 ± 0	16 ± 0	20.4 ± 0.89	- Nystatin (60 mg/ml): 32.2 ± 0.83, 34.8 ± 0.44, 35.8 ± 0.44, and 38.4 ± 1.34 mm, respectively	(57)
			<i>C. glabrata</i>	8 ± 0	16 ± 0	21.4 ± 0.54		
			<i>C. krusei</i>	8 ± 0	8 ± 0	23 ± 0.7		
			<i>C. guilliermondii</i>	8 ± 0	16 ± 0	23.2 ± 1.3		
		ZnNPs@Ziziphora (64 mg/ml)	<i>C. albicans</i>	0 ± 20	4 ± 0	37.6 ± 1.14	Efficacy of drugs on <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. krusei</i> , and <i>C. guilliermondii</i> in Disk diffusion: - Fluconazole (60 mg/ml): 40 ± 0.7, 42.8 ± 1.09, 43.4 ± 1.34, and 41.2 ± 0.44mm, respectively	(58)
			<i>C. glabrata</i>	0 ± 20	2 ± 0	36 ± 1		
			<i>C. krusei</i>	0 ± 10	1 ± 0	39.2 ± 0.83		
			<i>C. guilliermondii</i>	0 ± 10	2 ± 0	39.6 ± 1.14		
		<i>Z. clinopodioides</i> (64 mg/ml)	<i>C. albicans</i>	4 ± 0	8 ± 0	28.8 ± 1.09	- Amphotericin B (60 mg/ml): 35.6 ± 1.14, 41.4 ± 0.54, 40.8 ± 1.09, and 40 ± 0.7 mm, respectively	(58)
			<i>C. glabrata</i>	4 ± 0	4 ± 0	29.8 ± 0.44		
			<i>C. krusei</i>	0 ± 20	4 ± 0	32.6 ± 1.14		
			<i>C. guilliermondii</i>	0 ± 20	4 ± 0	30.8 ± 1.09		
		Zn(NO <sub>3</sub> )2.6H <sub>2</sub> O	<i>C. albicans</i>	16 ± 0	16 ± 0	19.6 ± 1.14	± 0.7 mm, respectively	

Aerial parts	Essential oil	-	(64 mg/ml)	<i>C. glabrata</i>	8 ± 0	16 ± 0	19 ± 1	- Nystatin (60 mg/ml): 37.4 ± 0.54, 40.4 ± 1.34, 40.4 ± 0.54, and 40.4 ± 1.34 mm, respectively	(59)
			<i>C. krusei</i>	4 ± 0	8 ± 0	21 ± 1			
			<i>C. guilliermondii</i>	8 ± 0	8 ± 0	19.6 ± 1.14			
			TiNPs@Ziziphora ( 64 mg/ml)	<i>C. albicans</i>	4 ± 0	4 ± 0	40.2 ± 0.83	Efficacy of drugs on <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. krusei</i> , and <i>C. guilliermondii</i> in Disk diffusion: - Fluconazole (60 mg/ml): 38.8 ± 0.44, 43.4 ± 1.34, 45.8 ± 0.44, and 46.8 ± 0.44mm, respectively - Amphotericin B (60 mg/ml): 35.4 ± 1.34, 39.8 ± 0.44, 38.4 ± 1.34, and 41.4 ± 1.34 mm, respectively - Nystatin (60 mg/ml): 33.8 ± 0.44, 36.2 ± 0.44, 38.2 ± 0.44, and 40.8 ± 0.44 mm, respectively	
				<i>C. glabrata</i>	2 ± 0	4 ± 0	43.8 ± 0.44		
				<i>C. krusei</i>	2 ± 0	2 ± 0	44.2 ± 0.44		
				<i>C. guilliermondii</i>	2 ± 0	4 ± 0	44.6 ± 1.14		
			<i>Z. clinopodioides</i> (64 mg/ml)	<i>C. albicans</i>	8 ± 0	8 ± 0	34.8 ± 0.44		
				<i>C. glabrata</i>	4 ± 0	8 ± 0	36.8 ± 1.09		
				<i>C. krusei</i>	4 ± 0	8 ± 0	37.8 ± 0.44		
				<i>C. guilliermondii</i>	4 ± 0	8 ± 0	36.4 ± 0.89		
			TiO2 (64 mg/ml)	<i>C. albicans</i>	8 ± 0	16 ± 0	22.2 ± 0.44		
				<i>C. glabrata</i>	8 ± 0	16 ± 0	23.2 ± 0.4		
				<i>C. krusei</i>	8 ± 0	16 ± 0	24.4 ± 0.89		
				<i>C. guilliermondii</i>	8 ± 0	16 ± 0	24.4 ± 1.34		
				<i>C. albicans</i>	0.56	0.1120	45	Efficacy of Amphotericin B, Ketoconazole and Nystatin: <b>MIC:</b> 2, 4 and 4 µg /ml, respectively <b>disk diffusion:</b> 16, 30 and 28 mm, respectively	(60)
			<i>Microsporum canis</i>	2 ± 0.6	2 ± 0.6	-			
			<i>Microsporum gypseum</i>	1 ± 0.4	2 ± 0.6	-			
				<i>Trichophyton rubrum</i>	2 ± 0.6	3 ± 0.9	-	Efficacy of drugs on <i>M. canis</i> , <i>M. gypseum</i> , <i>T. rubrum</i> , <i>T. mentagrophytes</i> , and <i>E. floccosum</i> in MIC (µg/ml): - Fluconazole: 0.5 ± 0.2, 0.25 ± 0.1, 4 ± 1.1, 2 ± 0.6, and 4 ± 1.1, respectively. - Terbinafine: 0.5 ± 0.2, 0.25 ± 0.1, 0.25 ± 0.1, 0.02± 0.01, and 0.5 ± 0.2, respectively	(61)
			<i>Trichophyton mentagrophytes</i>	1.5 ± 0.5	3 ± 0.9	-			
			<i>Epidermophyton floccosum</i>	2 ± 0.6	4 ± 1.1	-			
				<i>Microsporum canis</i>	0.01 µl/ml	0.03 µl/ml	-	-	(62)
			<i>Microsporum gypseum</i>	0.01 µl/ml	0.01 µl/ml	-			
			<i>Trichophyton rubrum</i>	0.06 µl/ml	0.06 µl/ml	-			

		<i>Trichophyton mentagrophytes</i>	0.03 μl/ml	0.03 μl/ml	-		
		<i>Trichophyton schoenleini</i>	0.01 μl/ml	0.01 μl/ml	-		
		<i>Aspergillus flavus</i>	48.82 μg/ml	781.25 μg/ml	-	-	(63)
			MIC <sub>90</sub> : 1.5	3	-	-	(64)
		<i>Aspergillus parasiticus</i>	48.82 μg/ml	390.625 μg/ml	-	-	(63)
			MIC <sub>90</sub> : 1.5	3	-	-	(64)
			MIC <sub>90</sub> : 2.1 ± 0.5	5.5 ± 2.8	-	-	(65)
	Aqueous extract	-	Has no effect	-	Has no effect		
	Ethanollic extract	-	250 μg/ml	-	10	<b>Nystatin</b> <b>MIC:</b> 31.25 μg /ml	(66)
	Acetonic extract	-	31.2 μg/ml	-	17	<b>Disk diffusion:</b> 18 mm	
	Chloroformic extract	-	62.5 μg/ml	-	17		



were inhibited the growth of *C. albicans* better than amphotericin B and nystatin. ZnNPs@*Ziziphora* antifungal effects were almost similar to fluconazole, amphotericin B, and nystatin on *C. albicans*, *C. glabrata*, *C. krusei*, and *C. guilliermondii* (58). Titanium nanoparticles of aqueous extract of *Z. clinopodioides* leaf (TiNPs@*Ziziphora*) were inhibited the growth of *C. albicans*, *C. krusei*, *C. glabrata*, and *C. guilliermondii* better than amphotericin B and nystatin. TiNPs@*Ziziphora* also were inhibited the growth of *C. albicans* and *C. glabrata* better than fluconazole (59). AgNPs@*Ziziphora*, MnNPs@*Ziziphora*, ZnNPs@*Ziziphora*, and TiNPs@*Ziziphora* had much higher effects in inhibiting different *Candida* species than nanoparticles and aqueous extract of *Z. clinopodioides* leaf. Also, aqueous extract of *Z. clinopodioides* leaf had higher activity than silver, magnesium, zinc and titanium nanoparticles and lower than positive controls (5, 57-59).

Essential oil of *Z. clinopodioides* aerial parts (EZA) inhibited the growth of *C. albicans* better than positive controls in minimum inhibitory concentration (MIC) and disk diffusion tests (60). EZA inhibited *T. rubrum*, *T. mentagrophytes*, and *E. floccosum* growth better than fluconazole in MIC test, but its effects were lower than terbinafine (61). Also, it has antifungal activity against *A. flavus*, *A. parasiticus*, *M. canis*, *M. gypseum*, and *T. schoenleini* (61-65).

Ethanollic, acetonic, and chloroformic extracts of *Z. clinopodioides* aerial parts had higher antifungal activity than nystatin in disk diffusion test against *C. albicans*. Also, the acetonic extract activity was similar to nystatin in MIC test. However, aqueous extract of *Z. clinopodioides* aerial parts had no activity against *C. albicans* in MIC and disk diffusion tests (66).

## Conclusion

Antifungal activities of *Z. clinopodioides* were summarized in this study. Silver, magnesium, zinc, and titanium nanoparticles of aqueous extract of *Z. clinopodioides* leaf

had significant antifungal activity against *C. albicans*, *C. glabrata*, *C. krusei*, and *C. guilliermondii*. Essential oil of *Z. clinopodioides* aerial parts can inhibit the growth of *A. flavus*, *A. parasiticus*, *C. albicans*, *E. floccosum*, *M. canis*, *M. gypseum*, *T. mentagrophytes*, *T. rubrum*, and *T. schoenleini*. Also, ethanollic, acetonic, and chloroformic extracts of *Z. clinopodioides* aerial parts had antifungal activity against *C. albicans*. In some studies, *Z. clinopodioides* effects were higher than standards (such as amphotericin B, fluconazole, nystatin, and terbinafine). Therefore, it seems that *Z. clinopodioides* can be a good choice for more experimental and clinical studies about fungal diseases.

## Conflicts of interest

The authors declare no conflict of interest.

## Funding

None has been declared.

## Authors' contributions

Design: M.H.H., and M.A.E.; Search: M.H.H. and M.E.; Data extraction: M.E., A.A., F.B., and M.H.H.; Writing the first draft: M.E., A.A., F.B., and M.H.H.; First revision: M.H.H.; Final revision: M.A.E.; supervision: M.A.E.; All authors read and approve the final version of the manuscript.

## References

- Hosseinzadeh MH, Ebrahimzadeh MA. Antioxidant Potential of *Ziziphora Clinopodioides* Lam: A Narrative Review. *Tabari Biomedical Student Research Journal*. 2020;2(2):7-1.
- Mozaffarian V. Identification of medicinal and aromatic plants of Iran: éditeur non identifié; 2013.
- Zhang X-M, An D-Q, Guo L-L, Yang N-H, Zhang H. Identification and screening of active components from *Ziziphora clinopodioides* Lam. in regulating autophagy. *Natural product research*. 2019;33(17):2549-

- 53.
4. Meral GE, Konyalioglu S, Ozturk B. Essential oil composition and antioxidant activity of endemic *Ziziphora taurica* subsp. *cleonioides*. *Fitoterapia*. 2002;73(7-8):716-8.
5. Ahmeda A, Zangeneh A, Kalbasi R, Seydi N, Zangeneh M, Mansouri S, et al. Green synthesis of silver nanoparticles from aqueous extract of *Ziziphora clinopodioides* Lam and evaluation of their bio-activities under in vitro and in vivo conditions. *Applied Organometallic Chemistry*. 2020;34(4):e5358.
6. Sonboli A, Mirjalili M, Hadian J, Ebrahimi S, Yousefzadi M. Antibacterial activity and composition of the essential oil of *Ziziphora clinopodioides* subsp. *bungeana* (Juz.) Rech. f. from Iran. *Zeitschrift fur Naturforschung C, Journal of Biosciences*. 2006;61(9-10):677-80.
7. Moran G, Coleman D, Sullivan D. An Introduction to the Medically Important *Candida* Species. *Candida and Candidiasis, Second Edition: American Society of Microbiology*; 2012. p. 11-25.
8. Lim CS-Y, Rosli R, Seow H, Chong P. *Candida* and invasive candidiasis: back to basics. *European Journal of Clinical Microbiology & Infectious Diseases*. 2012;31(1):21-31.
9. Tsai P-W, Chen Y-T, Hsu P-C, Lan C-Y. Study of *Candida albicans* and its interactions with the host: a mini review. *BioMedicine*. 2013;3(1):51-64.
10. Zida A, Bamba S, Yacouba A, Ouedraogo-Traore R, Guiguemdé R. Anti-*Candida albicans* natural products, sources of new antifungal drugs: A review. *Journal de mycologie medicale*. 2017;27(1):1-19.
11. Calugi C, Trabocchi A, Guarna A. Novel small molecules for the treatment of infections caused by *Candida albicans*: a patent review (2002–2010). *Expert opinion on therapeutic patents*. 2011;21(3):381-97.
12. Abbes S, Amouri I, Sellami H, Sellami A, Makni F, Ayadi A. A review of molecular techniques to type *Candida glabrata* isolates. *Mycoses*. 2010;53(6):463-7.
13. Rodrigues CF, Silva S, Henriques M. *Candida glabrata*: a review of its features and resistance. *European journal of clinical microbiology & infectious diseases*. 2014;33(5):673-88.
14. Krcmery V. *Torulopsis Glabrata* an Emerging Yeast Pathogen in Cancer Patients. *International journal of antimicrobial agents*. 1999;11(1):1-6.
15. Krcmery V, Barnes A. Non-*albicans* *Candida* spp. causing fungaemia: pathogenicity and antifungal resistance. *The Journal of Hospital Infection*. 2002;50(4):243-60.
16. Roetzer A, Gabaldón T, Schüller C. From *Saccharomyces cerevisiae* to *Candida glabrata* in a few easy steps: important adaptations for an opportunistic pathogen. *Fems Microbiology Letters*. 2011;314(1):1-9.
17. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC infectious diseases*. 2006;6(1):1-8.
18. Jamiu A, Albertyn J, Sebolai O, Pohl C. Update on *Candida krusei*, a potential multidrug-resistant pathogen. *Medical mycology*. 2021;59(1):14-30.
19. Gómez-Gaviria M, Mora-Montes HM. Current Aspects in the Biology, Pathogeny, and Treatment of *Candida krusei*, a Neglected Fungal Pathogen. *Infection and drug resistance*. 2020;13:1673-89.
20. Faria DR, Sakita KM, Capoci IRG, Arita GS, Rodrigues-Vendramini FAV, de Oliveira Junior AG, et al. Promising antifungal activity of new oxadiazole against *Candida krusei*. *Plos one*. 2020;15(1):e0227876.
21. Cheng J-W, Liao K, Kudinha T, Yu S-Y, Xiao M, Wang H, et al. Molecular epidemiology and azole resistance mechanism study of *Candida guilliermondii* from a Chinese surveillance system. *Scientific reports*. 2017;7(1):1-7.
22. Sanchis M, Pastor FJ, Capilla J, Sutton DA, Fothergill AW, Guarro J. Experimental therapy with azoles against *Candida guilliermondii*. *Antimicrobial agents and chemotherapy*. 2014;58(10):6255-7.
23. Santolaya ME, Matute TA, de Queiroz Telles F, Colombo AL, Zurita J,

- Tiraboschi IN, et al. Recommendations for the management of candidemia in neonates in Latin America. *Revista Iberoamericana de Micología*. 2013;30(3):158-70.
24. Tseng T-Y, Chen T-C, Ho C-M, Lin P-C, Chou C-H, Tsai C-T, et al. Clinical Features, Antifungal Susceptibility, and Outcome of *Candida guilliermondii* Fungemia: An Experience in a Tertiary Hospital in mid-Taiwan. *Journal of microbiology, immunology, and infection= Wei mian yu gan ran za zhi*. 2018;51(4):552-8.
25. Paredes K, Pastor FJ, Capilla J, Sutton DA, Mayayo E, Fothergill AW, et al. Therapies against murine *Candida guilliermondii* infection, relationship between in vitro antifungal pharmacodynamics and outcome. *Revista iberoamericana de micologia*. 2015;32(1):34-9.
26. Nakazawa H, Nishina S, Senoo Y, Sakai H, Ito T, Kikuchi K, et al. Breakthrough *Candida guilliermondii* (*Meyerozyma guilliermondii*) fungemia after cord blood transplantation for extranodal NK-cell lymphoma with azole prophylaxis. *Transplant Infectious Disease*. 2018;20(4):e12922.
27. Papon N, Savini V, Lanoue A, Simkin AJ, Crèche J, Giglioli-Guivarc'h N, et al. *Candida guilliermondii*: Biotechnological Applications, Perspectives for Biological Control, Emerging Clinical Importance and Recent Advances in Genetics. *Current genetics*. 2013;59(3):73-90.
28. Pasquetti M, Min ARM, Scacchetti S, Dogliero A, Peano A. Infection by *Microsporium Canis* in Paediatric Patients: A Veterinary Perspective. *Veterinary sciences*. 2017;4(3):46.
29. Aneke CI, Rhimi W, Hubka V, Otranto D, Cafarchia C. Virulence and Antifungal Susceptibility of *Microsporium canis* Strains from Animals and Humans. *Antibiotics*. 2021;10(3):296.
30. Watanabe J, Anzawa K, Mochizuki T. Molecular Epidemiology of Japanese Isolates of *Microsporium canis* Based on Multilocus Microsatellite Typing Fragment Analysis. *Japanese Journal of Infectious Diseases*. 2017;70(5):544-8.
31. Abastabar M, Jedi A, Guillot J, Ilkit M, Eidi S, Hedayati MT, et al. In vitro activities of 15 antifungal drugs against a large collection of clinical isolates of *Microsporium canis*. *Mycoses*. 2019;62(11):1069-78.
32. Aneke CI, Otranto D, Cafarchia C. Therapy and Antifungal Susceptibility Profile of *Microsporium canis*. *Journal of fungi* (Basel, Switzerland). 2018;4(3):107.
33. Romano C, Massai L, Gallo A, Fimiani M. *Microsporium gypseum* infection in the Siena area in 2005–2006. *Mycoses*. 2009;52(1):67-71.
34. Wang H, Yu C, Lu X, Wang S, Liu H, Zhang F. A case of subcutaneous infection caused by *Microsporium gypseum*. *Dermatologica sinica*. 2017;3(35):166-7.
35. Giudice MC, Reis-Menezes AA, Rittner GMG, Mota AJ, Gambale W. Isolation of *Microsporium Gypseum* in Soil Samples From Different Geographical Regions of Brazil, Evaluation of the Extracellular Proteolytic Enzymes Activities (Keratinase and Elastase) and Molecular Sequencing of Selected Strains. *Brazilian journal of microbiology:[publication of the Brazilian Society for Microbiology]*. 2012;43(3):895-902.
36. Bhagra S, Ganju S, Sood A, Guleria R, Kanga A. *Microsporium gypseum* dermatophytosis in a patient of acquired immunodeficiency syndrome: a rare case report. *Indian Journal of Medical Microbiology*. 2013;31(3):295-8.
37. Starace M, Carpanese MA, Alessandrini A, Piraccini BM, Patrizi A, Neri I. *Tinea corporis incognito* due to *Microsporium Gypseum*: Report of eight cases in children. *Pediatric Dermatology*.
38. Gupta A, Kar HK. Antidermatophytic activity of miconazole nanoformulation against *Trichophyton rubrum*. *Asian Pacific Journal of Tropical Disease*. 2015;5(9):707-10.
39. Pchelin IM, Azarov DV, Chilina GA, Dmitriev KA, Vasilyeva NV, Taraskina AE. Single-nucleotide polymorphism in a local

- population of *Trichophyton rubrum*. Medical mycology. 2018;56(1):125-8.
40. Akram MA, Khan BA, Khan MK, Alqahtani A, Alshahrani SM, Hosny KM. Fabrication and Characterization of Polymeric Pharmaceutical Emulgel Co-Loaded with Eugenol and Linalool for the Treatment of *Trichophyton rubrum* Infections. Polymers. 2021;13(22):3904.
  41. Gnat S, Łagowski D, Nowakiewicz A, Osińska M, Kopiński Ł. Population differentiation, antifungal susceptibility, and host range of *Trichophyton mentagrophytes* isolates causing recalcitrant infections in humans and animals. European Journal of Clinical Microbiology & Infectious Diseases. 2020;39(11):2099-113.
  42. Xiao C, Wang J, Liao Z, Huang Y, Ji Q, Liu Y, et al. Assessment of the mechanism of drug resistance in *Trichophyton mentagrophytes* in response to various substances. BMC Genomics. 2021;22(1):1-16.
  43. Shaw D, Singh S, Dogra S, Jayaraman J, Bhat R, Panda S, et al. MIC and Upper Limit of Wild-Type Distribution for 13 Antifungal Agents Against a *Trichophyton mentagrophytes*-*Trichophyton Interdigitale* Complex of Indian Origin. Antimicrobial agents and chemotherapy. 2020;64(4):e01964-19.
  44. Li H, Wu S, Mao L, Lei G, Zhang L, Lu A, et al. Human pathogenic fungus *Trichophyton schoenleinii* activates the NLRP3 inflammasome. Protein & cell. 2013;4(7):529-38.
  45. Mansouri P, Farshi S, Khosravi A, Naraghi Z, Chalangari R. *Trichophyton Schoenleinii*-induced widespread tinea corporis mimicking parapsoriasis. Journal De Mycologie Medicale. 2012;22(2):201-5.
  46. Belewa V, Baijnath H, Frost C, Somai B. *Tulbaghia violacea* Harv. plant extract affects cell wall synthesis in *Aspergillus flavus*. Journal of applied microbiology. 2017;122(4):921-31.
  47. Taghizadeh-Armaki M, Hedayati MT, Ansari S, Omran SM, Saber S, Rafati H, et al. Genetic diversity and in vitro antifungal susceptibility of 200 clinical and environmental *Aspergillus flavus* isolates. Antimicrobial agents and chemotherapy. 61(5):e00004-17.
  48. Tian J, Ban X, Zeng H, He J, Chen Y, Wang Y. The mechanism of antifungal action of essential oil from dill (*Anethum graveolens* L.) on *Aspergillus flavus*. PloS one. 2012;7(1):e30147.
  49. Hadrich I, Makni F, Neji S, Cheikhrouhou F, Sellami H, Ayadi A. A review molecular typing methods for *Aspergillus flavus* isolates. Mycopathologia. 2011;172(2):83-93.
  50. Chang P-K. Authentication of *Aspergillus parasiticus* strains in the genome database of the National Center for Biotechnology Information. BMC research notes. 2021;14(1):1-6.
  51. Horn BW, Ramirez-Prado JH, Carbone I. The sexual state of *Aspergillus parasiticus*. Mycologia. 2009;101(2):275-80.
  52. Youssef MM, Pham Q, Achar PN, Sreenivasa MY. Antifungal activity of essential oils on *Aspergillus parasiticus* isolated from peanuts. Journal of Plant Protection Research. 2016;56(2):139.
  53. Khosravi A, Behzad F, Sabokbar A, Shokri H, Haddadi S, Masoudi-Nejad A. Molecular typing of *Epidermophyton floccosum* isolated from patients with dermatophytosis by RAPD-PCR. Journal of basic microbiology. 2010;50(S1):S68-S73.
  54. Liu J, Ge L, Mei H, Zheng H, Peng J, Liang G, et al. Comparative Genomics and Molecular Analysis of *Epidermophyton floccosum*. Mycopathologia. 2021:1-11.
  55. Qiangqiang Z, Limo Q, Qixian Q. Case report. Disseminated tinea of the verrucous type due to *epidermophyton floccosum*. Mycoses. 2001;44(7-8):326-9.
  56. Ansari S, Ahmadi B, Norouzi M, Ansari Z, Afsarian MH, Lotfali E, et al. *Epidermophyton floccosum*: nucleotide sequence analysis and antifungal susceptibility testing of 40 clinical isolates. Journal of medical microbiology. 2019;68(11):1655-63.
  57. Mahdavi B, Paydarfard S, Zangeneh MM, Goorani S, Seydi N, Zangeneh A. Assessment of antioxidant, cytotoxicity,

antibacterial, antifungal, and cutaneous wound healing activities of green synthesized manganese nanoparticles using *Ziziphora clinopodioides* Lam leaves under in vitro and in vivo condition. *Applied organometallic chemistry*. 2020;34(1):e5248.

58. Mahdavi B, Saneei S, Qorbani M, Zhaleh M, Zangeneh A, Zangeneh MM, et al. *Ziziphora clinopodioides* Lam leaves aqueous extract mediated synthesis of zinc nanoparticles and their antibacterial, antifungal, cytotoxicity, antioxidant, and cutaneous wound healing properties under in vitro and in vivo conditions. *Applied Organometallic Chemistry*. 2019;33(11):e5164.

59. Seydi N, Mahdavi B, Paydarfard S, Zangeneh A, Zangeneh M, Najafi F, et al. Preparation, characterization, and assessment of cytotoxicity, antioxidant, antibacterial, antifungal, and cutaneous wound healing properties of titanium nanoparticles using aqueous extract of *Ziziphora clinopodioides* Lam leaves. *Applied Organometallic Chemistry*. 2019;33(9): e5009.

60. Shokri H, Sharifzadeh A, Tamai IA. Anti-Candida zeylanoides activity of some Iranian plants used in traditional medicine. *Journal de mycologie médicale*. 2012;22(3):211-6.

61. Khosravi RA, Shokri H, Farahnejat Z, Chalangari R, Katalin M. Antimycotic efficacy of Iranian medicinal plants towards dermatophytes obtained from patients with dermatophytosis. *Chinese journal of natural medicines*. 2013;11(1):43-8.

62. Mahboubi M, Tabar RH, Mahdizadeh E. Chemical composition and antifungal activities of *Ziziphora tenuior* and *Z. clinopodioides* essential oils against dermatophytes. *Herba Polonica*. 2018;64(2):37-45.

63. Moghadam HD, Sani AM, Sangatash MM. Antifungal activity of essential oil of *Ziziphora clinopodioides* and the inhibition of aflatoxin B1 production in maize grain. *Toxicology and industrial health*. 2016;32(3):493-9.

64. Khosravi A, Minooeianhaghighi M, Shokri H, Emami S, Alavi S, Asili J. The

potential inhibitory effect of *Cuminum cyminum*, *Ziziphora clinopodioides* and *Nigella sativa* essential oils on the growth of *Aspergillus fumigatus* and *Aspergillus flavus*. *Brazilian Journal of Microbiology*. 2011;42:216-24.

65. Khosravi AR, Shokri H, Minooeianhaghighi M. Inhibition of aflatoxin production and growth of *Aspergillus parasiticus* by *Cuminum cyminum*, *Ziziphora clinopodioides*, and *Nigella sativa* essential oils. *Foodborne pathogens and disease*. 2011;8(12):1275-80.

66. Unal EL, Mavi A, Kara AA, Cakir A, Şengül M, Yildirim A. Antimicrobial and antioxidant activities of some plants used as remedies in Turkish traditional medicine. *Pharmaceutical Biology*. 2008;46(3):207-24.