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

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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 schoenleini*. 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

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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

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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. schoenleiniiis* 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)

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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)	*C. albicans*	4 ± 0	4 ± 0	40 ± 1	Efficacy of drugs on C. albicans, C. glabrata, C. krusei, and C. guilliermondii in Disk diffusion: - Fluconazole (60 mg/ml): 38.6 ± 1.14, 44 ± 1.22, 42.2 ± 0.44, and 43 ± 0.7 mm, respectively - Amphotericin B (60 mg/ml): 36 ± 1.22, 42.8 ± 1.09, 40 ± 0.7, and 41.2 ± 0.83 mm, respectively - Nystatin (60 mg/ml): 35.2 ± 0.83, 39.6 ± 1.14, 39 ± 1.22, and 41 ± 0.7 mm, respectively	(5)
			C. glabrata	4 ± 0	4 ± 0	40 ± 1		
			C. krusei	2 ± 0	2 ± 0	43 ± 1		
			C. guilliermondii	2 ± 0	4 ± 0	44.2 ± 0.83		
		Z. clinopodioides (64 mg/ml)	*C. albicans*	8 ± 0	8 ± 0	34 ± 1.22		
			C. glabrata	8 ± 0	8 ± 0	35.6 ± 1.14		
			C. krusei	4 ± 0	8 ± 0	36.4 ± 0.89		
			C. guilliermondii	4 ± 0	8 ± 0	36.8 ± 1.09		
		AgNO3 (64 mg/ml)	*C. albicans*	16 ± 0	32 ± 0	23.4 ± 0.89		
			C. glabrata	16 ± 0	16 ± 0	22 ± 0.7		
			C. krusei	8 ± 0	16 ± 0	26 ± 0.7		
			C. guilliermondii	8 ± 0	16 ± 0	25.6 ± 0.89		
		MnNPs@Ziziphora (64 mg/ml)	*C. albicans*	4 ± 0	4 ± 0	38.4 ± 0.89	Efficacy of drugs on *C. albicans*, *C. glabrata*, *C. krusei*, and *C. guilliermondii* 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 - Amphotericin B (60 mg/ml): 36.2 ± 1.3, 41.6 ± 0.89, 38.4 ± 1.34, and 42.4 ± 0.89 mm, respectively - Nystatin (60 mg/ml): 32.2 ± 0.83, 34.8 ± 0.44, 35.8 ± 0.44, and 38.4 ± 1.34 mm, respectively	(57)
			C. glabrata	2 ± 0	4 ± 0	41.2 ± 1.3		
			C. krusei	1 ± 0	2 ± 0	44.4 ± 1.34		
			C. guilliermondii	2 ± 0	4 ± 0	42.2 ± 1.3		
		Z. clinopodioides (64 mg/ml)	*C. albicans*	4 ± 0	8 ± 0	29.4 ± 1.34		
			C. glabrata	4 ± 0	4 ± 0	29.8 ± 1.09		
			C. krusei	2 ± 0	2 ± 0	31 ± 1.22		
			C. guilliermondii	4 ± 0	4 ± 0	32.8 ± 0.44		
		MnSO4 (64 mg/ml)	*C. albicans*	16 ± 0	16 ± 0	20.4 ± 0.89		
			C. glabrata	8 ± 0	16 ± 0	21.4 ± 0.54		
			C. krusei	8 ± 0	8 ± 0	23 ± 0.7		
			C. guilliermondii	8 ± 0	16 ± 0	23.2 ± 1.3		
		ZnNPs@Ziziphora (64 mg/ml)	*C. albicans*	0 ± 20	4 ± 0	37.6 ± 1.14	Efficacy of drugs on *C. albicans*, *C. glabrata*, *C. krusei*, and *C. guilliermondii* in Disk diffusion: - Fluconazole (60 mg/ml): 40 ± 0.7, 42.8 ± 1.09, 43.4 ± 1.34, and 41.2 ± 0.44mm, respectively - Amphotericin B (60 mg/ml): 35.6 ± 1.14, 41.4 ± 0.54, 40.8 ± 1.09, and 40 ± 0.7 mm, respectively	(58)
			C. glabrata	0 ±20	2 ± 0	36 ± 1		
			C. krusei	0 ± 10	1 ± 0	39.2 ± 0.83		
			C. guilliermondii	0 ±10	2 ± 0	39.6 ± 1.14		
		Z. clinopodioides (64 mg/ml)	*C. albicans*	4 ± 0	8 ± 0	28.8 ± 1.09		
			C. glabrata	4 ± 0	4 ± 0	29.8 ± 0.44		
			C. krusei	0 ± 20	4 ± 0	32.6 ± 1.14		
			C. guilliermondii	0 ±20	4 ± 0	30.8 ± 1.09		
		Zn(NO3)2.6H2O	*C. albicans*	16 ± 0	16 ± 0	19.6 ± 1.14		

		(64 mg/ml)	*C. glabrata*	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	
			C. krusei	4 ± 0	8 ± 0	21 ± 1		
			C. guilliermondii	8 ± 0	8 ± 0	19.6 ± 1.14		
		TiNPs@Ziziphora (64 mg/ml)	*C. albicans*	4 ± 0	4 ± 0	40.2 ± 0.83	Efficacy of drugs on *C. albicans*, *C. glabrata*, *C. krusei*, and *C. guilliermondii* 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	(59)
			C. glabrata	2 ± 0	4 ± 0	43.8 ± 0.44		
			C. krusei	2 ± 0	2 ± 0	44.2 ± 0.44		
			C. guilliermondii	2 ± 0	4 ± 0	44.6 ± 1.14		
		Z. clinopodioides (64 mg/ml)	*C. albicans*	8 ± 0	8 ± 0	34.8 ± 0.44		
			C. glabrata	4 ± 0	8 ± 0	36.8 ± 1.09		
			C. krusei	4 ± 0	8 ± 0	37.8 ± 0.44		
			C. guilliermondii	4 ± 0	8 ± 0	36.4 ± 0.89		
		TiO2 (64 mg/ml)	*C. albicans*	8 ± 0	16 ± 0	22.2 ± 0.44		
			C. glabrata	8 ± 0	16 ± 0	23.2 ± 0.4		
			C. krusei	8 ± 0	16 ± 0	24.4 ± 0.89		
			C. guilliermondii	8 ± 0	16 ± 0	24.4 ± 1.34		
Aerial parts	Essential oil	-	*C. albicans*	0.56	0.1120	45	Efficacy of Amphotericin B, Ketoconazole and Nystatin: **MIC**: 2, 4 and 4 µg /ml, respectively **disk diffusion**: 16, 30 and 28 mm, respectively	(60)
			Microsporum canis	2 ± 0.6	2 ± 0.6	-	Efficacy of drugs on *M. canis*, *M. gypseum*, *T. rubrum*, T. mentagrophytes, and *E. floccosum* 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)
			Microsporum gypseum	1 ± 0.4	2 ± 0.6	-		
			Trichophyton rubrum	2 ± 0.6	3 ± 0.9	-		
			Trichophyton mentagrophytes	1.5 ± 0.5	3 ± 0.9	-		
			Epidermophyton floccosum	2 ± 0.6	4 ± 1.1	-		
			Microsporum canis	0.01 µl/ml	0.03 µl/ml	-	-	(62)
			Microsporum gypseum	0.01 µl/ml	0.01 µl/ml	-		
			Trichophyton rubrum	0.06 µl/ml	0.06 µl/ml	-		

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			Trichophyton mentagrophytes	0.03 µl/ml	0.03 µl/ml	-		
			Trichophyton schoenleini	0.01 µl/ml	0.01 µl/ml	-		
			Aspergillus flavus	48.82 µg/ml	781.25 µg/ml	-	-	(63)
				MIC_{90}: 1.5	3	-	-	(64)
			Aspergillus parasiticus	48.82 µg/ml	390.625 µg/ml	-	-	(63)
				MIC_{90}: 1.5	3	-	-	(64)
				MIC_{90}: 2.1 ± 0.5	5.5 ± 2.8	-	-	(65)
	Aqueous extract	-	*C. albicans*	Has no effect	-	Has no effect	**Nystatin** **MIC:** 31.25 µg /ml **Disk diffusion:** 18 mm	(66)
	Ethanolic extract	-		250 µg/ml	-	10		
	Acetonic extract	-		31.2 µg/ml	-	17		
	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).

Ethanolic, 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, ethanolic, 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.

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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.

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