MAEDICA – a Journal of Clinical Medicine
2022; 17(3): 647-653
https://doi.org/10.26574/maedica.2022.17.3.647

MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

Comparison of Antifungal Activity of Jaftex Mouthwash and Nystatin Suspension against the Growth of *Candida albicans*

Mansour AMIN[a], Fatemeh BABADI[b], Fatemeh MOTAHARI[c], Batool SADEGHI-NEJAD[d]

[a]Infectious and Tropical Diseases Research Center, Health Research Institute, Department of Microbiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[b]Department of Oral and Maxillofacial Medicine, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[c]School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[d]Abadan faculty of Medical Sciences, Abadan, Iran

ABSTRACT

Objective: *Oral candidiasis is an opportunistic fungal infection in the oral cavity caused by an overgrowth of* Candida *species, especially* Candida albicans. *Various herbal agents have been designed to target* Candida albicans. *The aim of this study was to evaluate the antifungal activity of Jaftex mouthwash and nystatin suspension on the growth of* Candida albicans.

Methods and materials: *In the present in vitro study, a standard strain of* Candida albicans *was prepared in the form of lyophilized ampoules. Jaftex mouthwash was prepared with an active ingredient (10 g* per *100 cc) of aqueous extract of oak fruit hull (Jaft),* Zataria multiflora *and* Satureja bachtiarica. *Nystatin oral suspension (100,000 IU/mL) was also prepared. Both mouthwashes were serially diluted using the two-fold serial dilution method (Jaftex: eight-fold dilutions; nystatin suspension: nine-fold dilutions). A volume of 10 µL of each dilution of Jaftex mouthwash and nystatin suspension was placed on the discs that were linearly inoculated on culture medium and stored in an incubator for 24 hours at 37 °C. The minimum inhibitory concentration (MIC) of the two antifungal agents was determined using the modified E-test. Data were analyzed using SPSS Version 26.0. A p-value less than 0.05 was considered statistically significant.*

Results: *The mean MIC values of Jaftex mouthwash and nystatin suspension were 0.0625 (mg/mL) and 0.0015 (mg/mL), respectively. There was a significant difference between the antifungal effect of Jaftex mouthwash and nystatin suspension on the growth of* Candida albicans. *Nystatin showed the lowest MIC and greater antifungal activity compared with Jaftex mouthwash.*

Conclusion: *Nystatin increasingly suppressed the growth of* Candida albicans. *Jaftex mouthwash inhibited the growth of* Candida albicans. *Since nystatin may show allergic reactions, Jaftex mouthwash can*

Address for correspondence:
Fatemeh Babadi, Assistant Professor
Department of Oral and Maxillofacial Medicine, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Article received on the 2nd of June 2022 and accepted for publication on the 16th of September 2022

be used as an alternative to nystatin. Due to the synergistic effect of nystatin with thymol, Jaftex mouthwash can be prescribed with nystatin.

Keywords: *Candida albicans*, mouth rinse, nystatin, multiflora, Satureja.

Abbreviations

Jaft: the inner layer of the oak
SDB: Sabouraud dextrose broth
SDA: Sabouraud dextrose agar
CFU: colony-forming unit
MIC: minimum inhibitory concentration
E-test: Epsilometer test
C. albicans: *Candida albicans*
AJUMS: Ahvaz Jundishapur University of Medical Sciences

INTRODUCTION

Candidiasis (yeast infections) refers to fungal infection caused by the genus Candida (1). The majority of opportunistic fungal infections in the oral cavity are caused by an overgrowth of Candida species (2). The prevalence of candidiasis is about 35% of the normal flora. *Candida albicans* (*C. albicans*) can become pathogenic under certain conditions, causing localized infections. There is a significant association between oral candidiasis and local predisposing factors (such as topical and inhaled corticosteroids, denture wearing, and smoking), and some systemic conditions that cause *Candida albicans* to become a pathogenic variant (3).

A marked growth and demand have been emerged in the use of medicinal plants globally. Medicinal plants have become popular due to a number of properties, including safety, free/few side effects, therapeutic effects, availability and affordability (4).

Antifungal polyenes such as nystatin are the main choice for the treatment of candidiasis (5). The use of nystatin has grown over the past years as a result of the augmented incidence of invasive fungal infections (6).

Nystatin-containing mouthwashes are used to prevent and treat fungal infections in patients with oral candidiasis. Although nystatin is considered the choice of therapy for oral candidiasis, it can cause side effects such as nausea, vomiting, diarrhea, mucosal irritation, and bitter taste. Furthermore, nystatin mouthwash has got bad marks or poor acceptance by patients (4, 7).

Jaftex is a new herbal mouthwash that contains an aqueous extract of oak fruit hull (Jaft) as the base and mixture of aqueous extract of *Zataria multiflora* and *Satureja bachtiarica*. Jaftex has been originally produced in the Medicinal Plants Research Center of Ahvaz Jundishapur University of Medical Sciences (AJUMS) (8).

The inner layer of the oak plant is called Jaft and has pharmaceutical and industrial applications. Earlier studies have reported the antifungal property of hydroalcoholic extract of Jaft (9). Similarly, *Zataria multiflora* and *Satureja bachtiarica* have the potential to inhibit the growth of *C. albicans* (10).

The aim of the present in vitro study was to compare the antifungal activity of Jaftex mouthwash and nystatin suspension against the growth of *C. albicans*. ❑

MATERIALS AND METHODS

Strains and culture conditions

The present in vitro study was carried out from March to April 2021 in the Microbiology Laboratory, Department of Microbiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Ethical considerations

The present study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Ethics ID: IR. AJUMS.REC. 1399.334).

Microbial sample preparation

Candida albicans standard strain (PTCC: 5027) was prepared in the form of lyophilized ampoules (inactive and powdered) from the Persian Type Culture Collection Center (Tehran, Iran).

Microorganism sampling, isolation, cultivation and characterization

A volume of 2 cc of Sabouraud dextrose broth (SDB) medium (Merck, Germany) was trans-

ferred to lyophilized vials and mixed. The microbial suspension was unloaded from lyophilized ampoules and transferred to Sabouraud dextrose agar (SDA) medium (Merck, Germany) for isolation of fungi and isolation and identification of *C. albicans* and incubated at 37°C for 24 hours. The plates containing soft agar grown colonies were preserved at -70°C after 24 hours of incubation. The 0.5 McFarland standard [1.5 x 108 colony forming units (CFU/mL)] bacterial suspensions were prepared.

Preparation of Jaftax mouthwash

Jaftex mouthwash with a patent number (139350140003008118) was prepared in the Medicinal Plants Research Center of Ahvaz Jundishapur University of Medical Sciences, Iran. The active ingredients of Jaftex mouthwash included 10 grams of oak fruit hull (Jaft) as the base and mixture of aqueous extract of *Zataria multiflora* and *Satureja bachtiarica*. The extraction process of each medicinal plant is further described. The oak fruit hull (Jaft) was washed with distilled water and dried at room temperature. The dried Jaft was powdered using a Multi-functional Grinder Machine. The prepared powder was poured into a double-layered bag and placed in an Erlenmeyer flask containing 150 mL of distilled boiling water. The solution was vibrated for 24 hours on the low-speed setting. The resulting extract was filtered through Whatman No.1 filter and then centrifuged at 2400 rpm for 10 min. The resulting clear liquid was then stored at 4 °C in a dark container. Similarly, the aqueous extract of *Zataria multiflora* and *Satureja bachtiarica* were prepared according to Jaft extraction method. In the last step, the aqueous extracts of the three plants were mixed together and the resulting solution was increased to a volume of 100 mL with distilled water and stored in the refrigerator.

Preparation of nystatin suspension

Nystatin oral suspension, 100,000 USP Nystatin Units per mL (Emad Darman, Pars Co., Saveh, Iran), was obtained. To prepare an oral suspension, the closed bottle was tapped several times to loosen powder. In the next step, cooled boiled water was added to powder until the fill-mark on the bottle. The bottle was shaken well to obtain uniform suspension(100,000IU/mL=17.51mg/mL) and stored in a refrigerator (at 4 °C) for the post-analytical phase.

Susceptibility test method

Both mouthwashes were serially diluted using the two-fold serial dilution method (Jaftex: eight-fold dilutions; nystatin suspension: nine-fold dilutions); with this procedure, the concentration of both mouthwashes was lowered by a factor of two that reduced the original concentration by one half. Immediately, the blank disks were placed in two Petri dishes (eight disks for Jaftex and nine for nystatin) containing the culture medium inoculated with the target fungus in a straight line from top to bottom. In the next phase, 10 µL of each dilution of Jaftex mouthwash and nystatin suspension were placed on the discs that were linearly inoculated on the culture medium. In the Petri dish containing Jaftex, disk No. 8 treated with sterile distilled water was considered as negative control. In the Petri dish containing nystatin suspension, the disk treated with sterile distilled water was considered as negative control and disc No. 1 containing pure nystatin was considered as positive control. The Petri dishes were stored in an incubator for 24 hours at 37 °C.

Measurement of MIC

The MIC value is the lowest concentration on a disk for which no growth is observed (11). The MIC of the two antifungal agents was determined through the modified E-test, in which several discs previously injected with different dilutions of mouthwash were used instead of strips. In

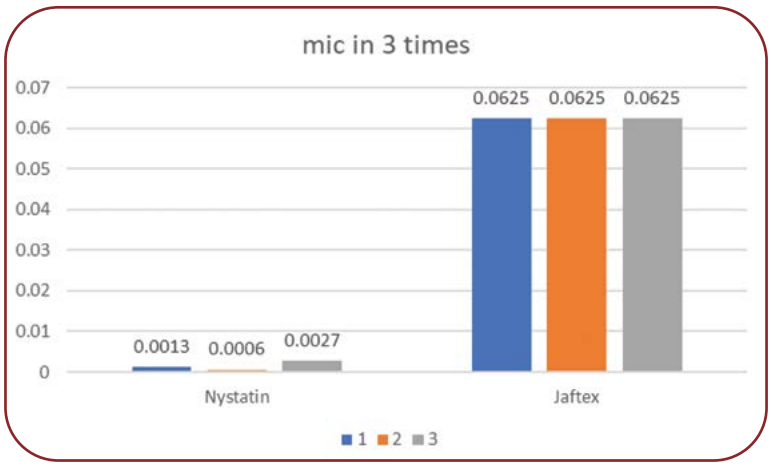

FIGURE 1. The effect of Jaftex herbal mouthwash and nystatin suspension on *Candida albicans* using the modified E-test method

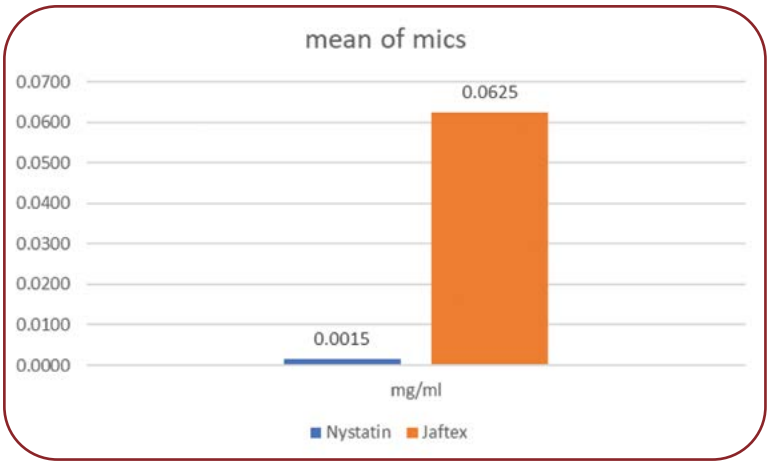

FIGURE 2. Mean ± standard deviation of MIC values of Jaftax herbal mouthwash and nystatin suspension against *Candida albicans* using the modified E-test method

fact, the modified E-test method is a simulated version of the standard E-test procedure (12). In order to avoid any errors and ensure consistency in the resulting data, the experiment was repeated three times. The mean MIC was calculated for Jaftex mouthwash and nystatin suspension (10 µL of solution was reported as MIC in mg/mL) (Figures 1 and 2).

Data analysis

Evaluation of fungal colony and bacterial growth was done with the naked eye. Descriptive statistics were used to summarize the characteristics of the data set. The Mann-Whitney U test was used for comparison of the median values in the two study groups. Data were analyzed using SPSS (SPSS, Inc., Chicago, IL, USA) Version 26.0. A p-value less than 0.05 (typically ≤ 0.05) was considered statistically significant. ❑

RESULTS

In this study, eight concentrations of Jaftex and nine concentrations of nystatin against *C. albicans* were determined in order to find the MIC of Jaftex mouthwash and nystatin suspension. The concentration of each disk was calculated. The lowest concentration (in mg/mL) value (MIC) of the two agents that inhibited the growth of *C. albicans* is presented in Tables 1 and 2. The mean MIC values of Jaftex mouthwash and nystatin suspension were 0.0625 (mg/mL) and 0.0015 (mg/mL), respectively (Table 3). There was a significant difference between the antifungal effect of Jaftex mouthwash and nystatin sus-

Groups	Test	MIC (mg/mL)							
		1	0.5	0.75	0.125	0.0625	0.03125	0.015625	0
		Disc 1	Disc 2	Disc 3	Disc 4	Disc 5	Disc 6	Disc 7	Disc 8
Jaftex	First	-	-	-	-	+*	+	+	+
	Second	-	-	-	-	+	+	+	+
	Third	-	-	-	-	+	+	+	+
(*) the lowest concentration (MIC); (-) no fungal growth; (+) fungal growth									

TABLE 1. The effect of Jaftex herbal mouthwash on *Candida albicans* using the modified E-test method

Groups	Test	MIC (mg/mL)									
		0.1751	0.0875	0.0437	0.0218	0.0109	0.0054	0.0027	0.0013	0.0006	0
		Disc 1	Disc 2	Disc 3	Disc 4	Disc 5	Disc 6	Disc 7	Disc 8	Disc 9	Disc 10
Nystatin	First	-	-	-	-	-	-	-	*+	+	+
	Second	-	-	-	-	-	-	-	-	+*	+
	Third	-	-	-	-	-	-	*+	+	+	+
(*) the lowest concentration (MIC); (-) no fungal growth; (+) fungal growth											

TABLE 2. The effect of nystatin suspension on *Candida albicans* using the modified E-test method

Groups	Number	Mean ± SD of MIC	Test statistics	P-value
Jaftex	3	0.0625 ± 0.0000	3.000	0.037
Nystatin	3	0.0015 ± 0.0011		

TABLE 3. Mean ± standard deviation of MIC values of Jaftax herbal mouthwash and nystatin suspension against *Candida albicans* using the modified E-test method

pension on the growth of *Candida albicans*. Nystatin had the lowest MIC and greater antifungal activity compared with Jaftex mouthwash (Table 3). ❑

DISCUSSION

Nowadays, medicinal plants are widely used due to the potential side effects of synthetic drugs (13). The antifungal activity of herbal medicines against *Candida* species has been addressed in several studies (14).

The aim of the present in vitro study was to compare the antifungal activity of Jaftex mouthwash and nystatin suspension against the growth of *C. albicans*. Our findings showed that both Jaftex mouthwash and nystatin suspension had antifungal activity against the growth of *C. albicans*. However, the antifungal activity of nystatin suspension (MIC=0.0015 mg/mL) was more than Jaftex mouthwash (MIC 0.0625 mg/mL).

Nystatin is commercially produced by the bacterium Streptomyces noursei. Nystatin has been shown to have a broad anti-*Candida* activity. The mechanism of action of nystatin is to bind the ergosterol of the fungal plasma membrane. Moreover, it forms pores which promote intracellular potassium leakage and impair fungal viability (15).

Gonoudi *et al* compared the antifungal efficiency of *Zataria multiflora* and nystatin suspension for the treatment of denture stomatitis and concluded that *Zataria multiflora* drop and nystatin drop were more effective in the resolution of palatal erythematous lesions and decrease of *C. albicans* colony count (4).

Jaftex is a new herbal mouthwash that contains an aqueous extract of oak fruit hull (Jaft) as the base and mixture of aqueous extract of *Zataria multiflora* and *Satureja bachtiarica*. Baghipour *et al* evaluated the effect of Jaftex mouthwash on the growth of *C. albicans* and *Candida tropicalis* using the modified E-test and suggested that Jaftex mouthwash inhibited the growth of *C. albicans* and *C. tropicalis* and can be used for treatment of oral candidiasis (16).

The antifungal activity of Jaftex mouthwash has not yet been addressed in previous studies. However, the antifungal activity of the active ingredients of Jaftex mouthwash has been documented.

Sharifi *et al* studied the antifungal properties of Quercus infectoria gall (oak) on Saproling fungi and concluded that the hydro-alcoholic extract of Jaft (oak fruit) can inhibit fungal growth. Tannins, which are mostly found in Jaft extract, have antifungal properties. In addition, the toxicity of tannins to bacteria, yeasts, and filamentous fungi has been recognized. Tannins can inhibit the growth of microbes by a variety of mechanisms, including deposition of microbial proteins and protection of dietary protein from microbial degradation (9).

Naeini *et al* studied the anti-*Candida* effects of essential oil and extracts of 50 species of Iranian medicinal plants. Their results revealed a potent anti-*Candida* activity of the essential oil and extract of *Zataria multiflora* against the strain of *Candida albicans*. However, the essential oil of *Zataria multiflora* was reported to be more active than the extract of *Zataria multiflora*. In the same study, *Zataria multiflora* was one of the plants that showed stronger anti-*Candida* effects compared to nystatin, amphotericin B, and clotrimazole (17).

Rahimi *et al* evaluated the antifungal effects of ethanolic and aqueous extracts of *Zataria multiflora* against the pathogenic yeast *Candida albicans* and concluded that *Zataria multiflora* could inhibit the growth of *Candida albicans*. Moreover, ethanolic extracts of *Zataria multiflora* were shown to display a stronger antifungal activity than aqueous extracts (18).

Rohi Boroujeni *et al* examined the anti-*Candida* activity of ethanolic extracts of Iranian endemic medicinal herbs, including *Satureja bachtiarica*, and concluded that the extract of *Satureja bachtiarica* could inhibit the growth of *Candida albicans* and might be a useful natural anti-*Candida* agent (19).

Pirbalouti evaluated the anti-*Candida* activities of extracts and essential oils of some Iranian folklore plants, among which *Satureja bachtiarica*, known for containing significant amounts of phenolic compounds, was found to exhibit an inhibitory effect on the growth of *Candida albicans* (20).

Carvacrol and thymol are the main ingredients of *Zataria multiflora* (21). Carvacol is also the main phenolic compound of *Satureja bachtiarica* (19). Thymol and carvacrol are isomers with similar chemical mechanisms (22). Carvacrol is an iso-thymol that upsurges the activity of ATP-ase

and prevents the activity of the enzyme responsible for non-specific penetrability of the cell membrane of microorganisms (23). The antifungal activity of carvacrol has been documented in previous studies (18-21).

Thymol is a phytoconstituent and is classified as a monoterpene (14). Some studies have shown that it had a broad spectrum of biological activity. Additionally, previous studies described its antiseptic, anti-inflammatory and antioxidant activity (24, 25). Thymol has been shown to display antifungal activity against strains of *Candida* species. The combination of thymol and nystatin inhibits the growth of *Candida* species by influencing the fungal cell membrane and producing a synergistic effect (26).

Recommendation

It is recommended to compare the Jaftex mouthwash with other Azole antifungals and herbal mouthwashes. ❑

CONCLUSION

Nystatin has increasingly suppressed the growth of *Candida albicans*, while Jaftex mouthwash inhibited the growth of *C. albicans*. Since nystatin may cause allergic reactions, Jaftex mouthwash can be used as an alternative to nystatin. Due to the synergistic effect of nystatin with thymol, Jaftex mouthwash can be prescribed with nystatin. ❑

Conflicts of interest: none declared.

Financial support: The present study was supported by grant No: OG-9916, Vice Chancellor for Research affairs and the Infectious and Tropical Diseases Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Ethics approval and participation consent: This study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Code of: IR. AJUMS.REC. 1399.334).

Availability of data and materials: The datasets used and analyzed during the current study are not publicly available due to further studies related to the data but are available from the corresponding author on reasonable request.

Authors' contributions: Mansour Amin, Fatemeh Babadi, Fatemeh Motahari were involved in methodology, data curation, formal analysis and writing of the original draft. Batool Sadeghi Nejad was responsible for the methodology and writing of the original draft.

Acknowledgments: The present study was part of the doctoral thesis of Fatemeh Motahari and was approved by Ahvaz Jundishapur University of Medical Sciences. The authors are grateful to the Vice Chancellor for Research Affairs and the Infectious and Tropical Diseases Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

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