Frontiers in Dentistry

Antifungal Efficacy of *Ganoderma lucidum* and Clotrimazole for Treatment of Denture Stomatitis: A Randomized Clinical Trial

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Article Info

Article type:
Original Article

Article History:
Received: 20 Nov 2023
Accepted: 05 May 2024
Published: 01 Dec 2024

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A B S T R A C T

Objectives: This study aimed to compare the antifungal efficacy of *Ganoderma lucidum* (*G. lucidum*) and clotrimazole for treatment of denture stomatitis (DS).

Materials and Methods: This double-blind randomized clinical trial was conducted on 50 patients with DS types I and II assigned to two groups (N=25). In the first group, *G. lucidum* extract was administered in the form of 5% gel while 1% clotrimazole gel was prescribed for the second group. Pain intensity according to the visual analog scale (VAS), and the percentage of DS recovery based on the Budtz-Jorgenson index were evaluated and recorded after 7 and 14 days. Data were analyzed using the Chi-square test, independent samples t-test, repeated measures ANOVA, and logistic regression (alpha=0.05).

Results: The percentage of complete recovery on day 7 in the *G. lucidum* group (28%) was higher than that in the clotrimazole group (16%) but not significantly (P=0.592). Not wearing dentures overnight significantly increased the odds of recovery by 6.56 times, while the odds of recovery decreased by 0.03 times in DS type II, as compared to DS type I (P= 0.009).

Conclusion: No significant difference existed between the antifungal efficacy of *G. lucidum* and clotrimazole for clinical treatment of DS. Thus, Ganoderma may be regarded as an alternative treatment, especially in patients' resistant to azoles. Nonetheless, further clinical studies are required to shed more light on this topic.

Keywords: Reishi; Clotrimazole; Antifungal Agents

➢ **Cite this article as:** Pakravan F, Yegdaneh A, Taymori S, Rahimi Sh, Ghahremani N. Antifungal Efficacy of *Ganoderma lucidum* and Clotrimazole for Treatment of Denture Stomatitis: A Randomized Clinical Trial. *Front Dent*. 2024:21:45.

INTRODUCTION

Candida-associated denture stomatitis (DS) is the most common form of oral candidiasis [1]. It is a chronic inflammatory disease that affects the mucosa under removable dentures, particularly complete maxillary dentures, with a prevalence rate of 11%-67%. This inflammatory condition can cause symptoms such as erythema, swelling of the mucous membranes, and occasional pain and burning sensation [1-3]. DS is a multifactorial disease, and poor denture hygiene and its suboptimal adaptation, diabetes mellitus, smoking, allergies, nutrition, and multiple microorganisms have been suggested as its common etiologies. However, *Candida*

albicans (*C. albicans*) remains the principal etiological agent for DS [3].

Candida species are round-to-oval yeasts, with asexual reproduction through the germination process [4]. More than 100 species of Candida have been identified. However, only a few have been isolated from humans, and *C. albicans* remains the most common cause of fungal disease in humans due to its high pathogenicity [5].

One of the most commonly used classifications of DS was presented by Av [6] and Ostlund [7], which includes three types: Type I is DS with hyperemic foci, type II is DS with diffuse hyperemia, and type III is DS with granular inflammation. DS is generally followed by erythema, swelling of the oral mucosa, and occasional pain or burning sensation [8].

Elimination of predisposing factors is the first strategy in treatment of oral candidiasis, and various topical and systemic agents are currently available for this purpose [9]. Topical agents such as nystatin, amphotericin B, miconazole, and clotrimazole are recommended as the first-line treatment [9].

Clotrimazole is well tolerated by patients and has insignificant complications. However, drug resistance is quite common in immunocompromised patients [10]. Also, a recent investigation elaborated on some adverse effects of clotrimazole such as burning sensation and occasional skin irritation [11]. In addition, it has been discovered that other microbial agents, including Streptococcus and Lactobacillus species, may accompany *C. albicans*.

Ganoderma lucidum (*G. lucidum*), also known as lingzhi, is one of the most valuable and well-known fungi, which is predominantly used in Asia for various medicinal purposes, and has more than 300 species [12]. Furthermore, it is classified as a "superior herb" that can be used continuously without any complications [13]. The health effects of *G. lucidum* comprise antifungal, antiviral, antioxidant, antitumor, immune booster, and antidiabetic effects. Despite the significant health benefits of *G. lucidum*, its underlying mechanism of action has not been well elucidated [13].

Triterpenoids and polysaccharides have been noted as the most important pharmacological components of Ganoderma. Triterpenoids have anti-inflammatory, anti-hypertensive, anti-cholesterol, anti-liver fibrosis, antitumor, anti-aging, and immunomodulatory effects. In addition, polysaccharides have protective effects against free radicals [14]. Ganoderma is one of the proteins isolated from the fruiting body of *G. lucidum*, which has antifungal activity [15].

Considering the drug resistance patterns and complications of the standard treatments for DS, and scarcity of studies addressing the antifungal effects of *G. lucidum*, the present study aimed to evaluate the antifungal efficacy of *G. lucidum* gel, compared with clotrimazole gel, for treatment of DS.

MATERIALS AND METHODS

Study design and patients:

This double-blind randomized clinical trial was conducted on 50 patients with complete removable maxillary acrylic dentures who had the manifestations of DS type I or II according to the Av [6] and Ostlund [7] classification, and referred to the Department of Oral and Maxillofacial Pathology of Isfahan Dental School during 2018-2019. The study was approved by the ethics committee of Isfahan University of Medical Sciences (approval code: IR.MUI.RESEARCH.REC.1398.796), and registered in the Iranian Registry of Clinical Trials (registration number: IRCT20200303046685N2). The patients were excluded from the study if they had a recent history of using antifungal or antibacterial drugs or corticosteroids [16]. Other exclusion criteria were hypersensitivity to *G. lucidum* or clotrimazole, immune-deficiency, Alzheimer's disease, neuromuscular diseases, mental disorders, poor cooperation [8], history of previous or current head and neck radiotherapy, history of previous or current chemotherapy [16], ill-fitted or discolored denture, problems with the muscles of mastication [8], and uncontrolled diabetes mellitus [17].

After obtaining written informed consent from eligible patients, 50 patients were selected by convenience sampling and were divided into two groups (N=25) using a random allocation software (Figure 1). In order to control for the

confounding factors such as eating habits and personal hygiene, all patients were given the same diet and denture hygiene instructions. The standardized diet included balanced meals with specific macronutrient ratios, reducing sugar intake, emphasizing on the consumption of soft, non-irritating foods like oatmeal, grilled chicken, and steamed vegetables, and avoiding spicy or acidic foods. This approach was adopted to ensure consistent nutritional intake while minimizing factors that could influence oral inflammation and treatment outcomes [18]. At the beginning of the study, patients' demographic and clinical parameters including their age, sex, smoking status, duration of denture use, sleeping habits (with/without denture), daily cleaning of denture, and degree of inflammation based on the Av [6] and Ostlund [7] classification were recorded.

Preparation of medicinal gels:

The *G. lucidum* samples were ground, and extraction was performed using the maceration technique using hydroalcoholic solvent (10% water and 70% ethanol) [12,19]. To prepare 2% w/w sodium carboxymethylcellulose (CMC) gel, specific amounts of powder were weighed and then dispersed in water on a magnetic stirrer. Also, 0.18% w/w methylparaben and 0.02% w/w propylparaben were used as preservatives in the gel formulation. To prepare 100g of 1% w/w clotrimazole gel, 1g of clotrimazole powder was diluted with a certain amount of propylene glycol and then added to CMC gel. To prepare 100g Ganoderma gel (5% w/w), 5g of *G. lucidum* extract was diluted with a certain amount of propylene glycol and then added to CMC gel. Finally, the medicinal gels were packed in similar packaging in terms of shape, color, and size at the Department of Pharmacognosy, Faculty of Pharmacy, Isfahan University of Medical Sciences.

Intervention:

At the beginning of the intervention, as mentioned before, all patients were given the same nutritional program and health instructions. The frequency of food consumption was also included in the provided nutritional program.

The treatment group received 5% *G. lucidum* extract while the control group received 1% clotrimazole gel. The patients were not allowed to use any analgesics, non-steroidal anti-inflammatory drugs, or liquid morphine before or during the study to prevent their confounding effects on the VAS score. After each meal (i.e., three times a day) and for two consecutive weeks, all patients or their caregivers were asked to practice oral hygiene and denture care by thoroughly cleaning their mouth, cleaning the tissue side of their dentures and its other parts with a soft toothbrush and liquid soap, and 0.12% chlorhexidine. They were asked to apply a thin layer of gel on the tissue side of the denture after cleaning it and then wear it. Moreover, they were requested to remove the denture every night and keep it in a water container overnight [16]. The treatment was discontinued in case of severe complications or upon patient's request. Each treatment modality was discontinued in case of complete response, and continued for another week if improvement without full resolution of symptoms and lesions was ascertained [20].

Blinding:

G. lucidum and clotrimazole gels had the same appearance, color, and volume, and the same packages labeled as A and B with the appropriate prescription of each gel placed inside the package. A researcher delivered the gels to the patients and instructed them on how to use the gels without knowing the type. In addition, the patients and the clinical outcome assessor were blinded to the type of gel.

Outcome measures:

The patients' pain score and recovery rate were evaluated at baseline, and 7 and 14 days after the intervention. The patients' pain and burning sensation were quantified using a visual analog scale (VAS) with score 0 indicating no pain to score 10 indicating maximum pain. The index suggested by Budts-Jorgensen et al. [21] was also used to score clinical improvements such that score 0 indicated complete recovery (no inflammation), score 1 showed partial

recovery (reduction of inflammation), and score 2 indicated no recovery (no change in inflammation) [22].

Statistical analysis:

Data were recorded and analyzed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). The Chi-Square test was used to compare the frequency distribution of qualitative data (such as sex, duration of denture use, smoking, sleeping with denture, daily cleaning of denture, Av [6] and Ostlund [7] classification, and recovery level) between the two groups, and independent samples t-test was used to compare the mean quantitative data (such as age, and pain score) between the two groups. Repeated measures ANOVA was used for evaluation of the trend of change in the mean pain score over time in each of the two groups. Also, the Wilcoxon test was used to compare the recovery at 14 days after the intervention, as compared to 7 days after the intervention. Moreover, logistic regression (enter method) was used to investigate the factors associated with resolution of DS. Additionally, the odds ratios (ORs) were reported. In all analyses, a significance level of 0.05 was considered.

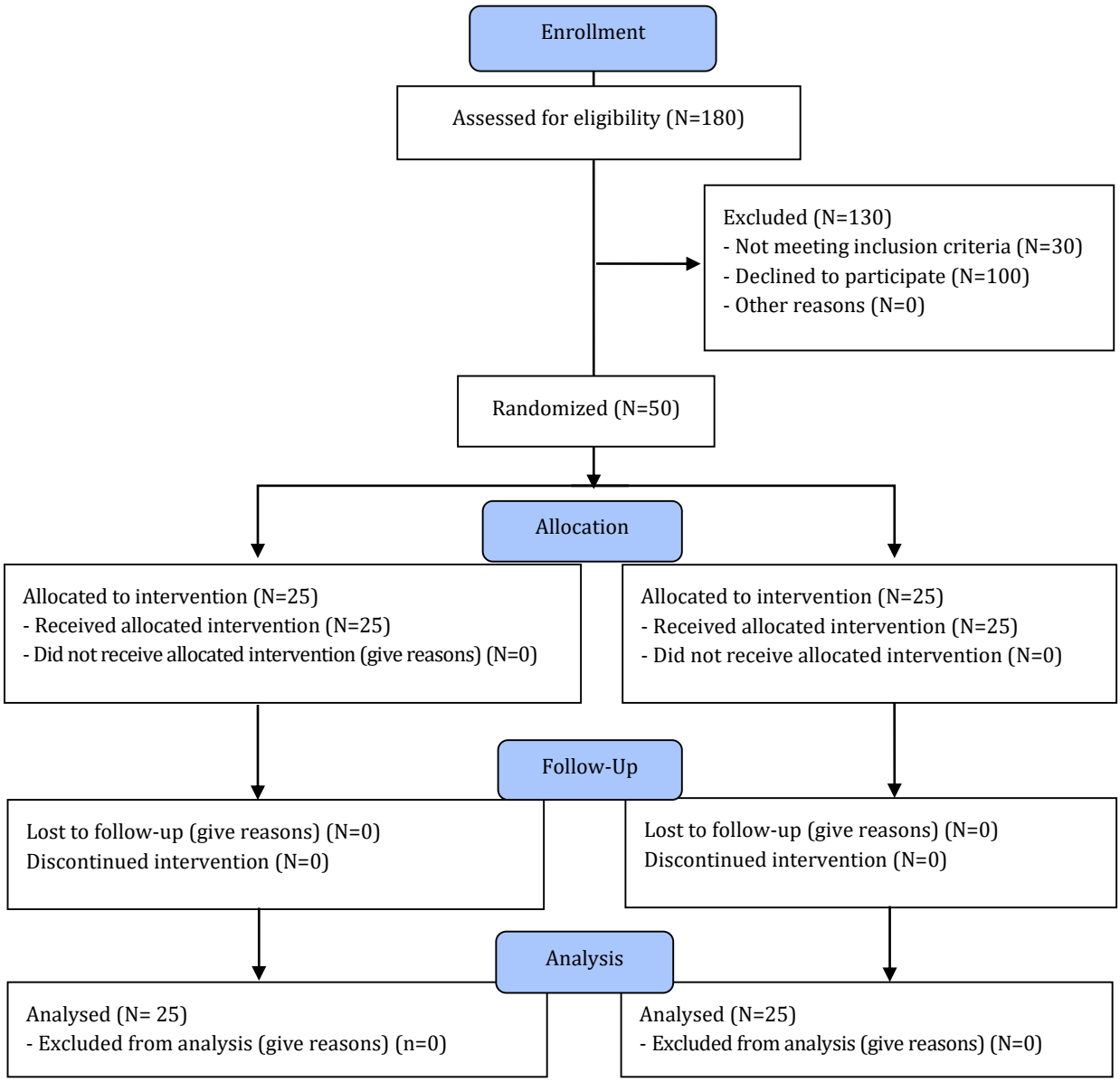

Fig. 1: Consort flow-diagram of patient selection and allocation

RESULTS

In the present study, out of 25 patients in the *G. lucidum* group with a mean age of 70.52±12.70 years, 12 (48%) patients were males and 13 (52%) were females. In the clotrimazole group, the mean age was 63.56±12.21 years, and patients consisted of 15 (60%) males and 10 (40%) females (P>0.05). Moreover, there was no significant difference in smoking status, duration of denture use, sleeping with denture, daily cleaning of denture, or the Av [6] and Ostlund [7] classification between the two groups (P>0.05, Table 1).

Table 1. Patients' demographic and clinical characteristics in the two groups (N=25, each)

Variables	*G. Lucidum*	Clotrimazole	P
Sex			
Male	12(48)	15(60)	0.571[a]
Female	13(52)	10(40)	
Age (y)	70.52±12.70	63.56±12.21	0.064[b]
Duration of denture use (y)			
1-5	17(68)	12(48)	
5-10	5(20)	5(20)	0.083[a]
>10	3(12)	8(32)	
Smoking	4(16)	7(28)	0.306[a]
Sleeping with denture	17(68)	16(64)	0.996[a]
Daily cleaning of denture			
No	10(40)	7(28)	
Once	11(44)	11(44)	0.510[a]
≥Twice	4(16)	7(28)	
Av and Ostlund classification			
Type I	12(48)	14(56)	0.778[a]
Type II	13(52)	11(44)	

Data are shown as mean±standard deviation or number (%)
[a] Chi-square test ;[b] Independent samples t-test

There was no significant difference between the two groups in terms of the mean pain score before the intervention and at 7 and 14 days after the intervention (P>0.05); however, a significant reduction in pain score was reported in each of the two groups over the 14-day intervention period (P<0.001). Although the percentage of complete recovery in the *G. lucidum* group was higher than that in the clotrimazole group, this difference was not significant (P=0.592). During the 14-day intervention period, a significant improvement was reported in patients' recovery in both groups (P=0.001; Figure 2, Table 2).

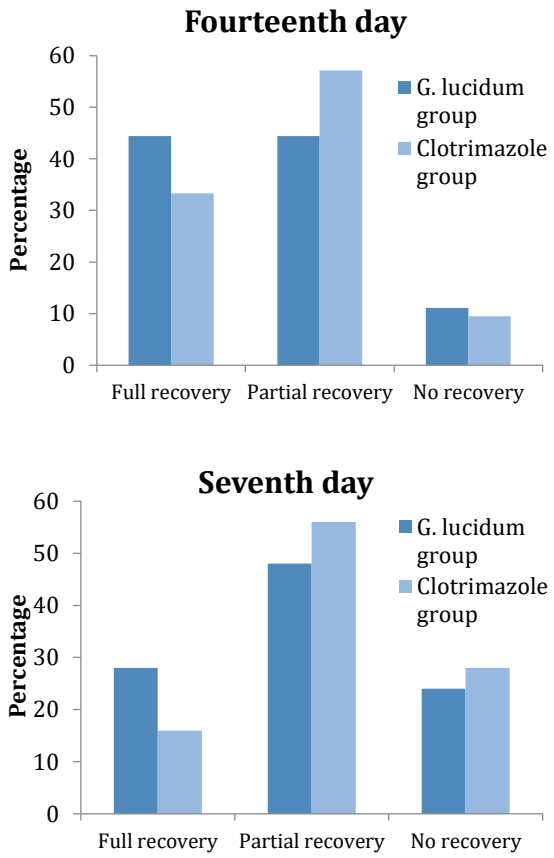

Fig. 2. Frequency of patients' recovery at 7 and 14 days after the intervention in the two groups

Evaluation of the factors associated with complete recovery of DS revealed that the recovery rate in the clotrimazole group was lower than the recovery rate in the *G. lucidum* group; however, this difference was not statistically significant (P=0.054, OR: 0.21, 95% CI: 0.03-1.45). Moreover, female sex, aging, increased duration of denture use, and smoking were associated with lower recovery rate although this association was not significant (P>0.05). In contrast, removing denture overnight significantly increased the odds of recovery (OR: 6.56, 95% CI: 1.12-18.11). Also, the odds of recovery were lower in DS type II, as compared to DS type I (P= 0.009, OR: 0.03, 95% CI: 0.01-0.23, Table 3).

Table 2. Comparison of recovery percentage and mean pain score at 7 and 14 days after the intervention in the two study groups (N=25, each)

Outcome	*G. lucidum*	Clotrimazole	P
Pain			
Baseline	7.32±1.62	7.85±1.47	0.232[a]
Day 7	4.98±1.11	5.38±1.78	0.345[a]
Day 14	3.23±1.06	3.75±1.58	0.178[a]
P[b]	<0.001	<0.001	
Day 7 recovery			
Full	7.25 (28%)	4.25 (16%)	0.592[c]
Partial	12.25 (48%)	14.25 (56%)	
None	6.25 (24%)	7.25 (28%)	
Day 14 recovery			
Full	8.18 (44.4%)	7.21 (33.3%)	0.726[c]
Partial	8.18 (44.4%)	12.21 (57.1%)	
None	2.18 (11.1%)	2.21 (9.5%)	
P[d]	0.001	0.001	

Data are shown as mean±standard deviation or number (%)
[a] Independent samples t-test; [b] Repeated measures ANOVA (trend of change in mean pain score over time); [c] Chi-square test; [d] Wilcoxon test to compare recovery at two time points

Table 3. Determination of risk factors associated with patients' complete recovery

Factors	OR	95% (CI)	P
Groups			
G. lucidum	Reference	-	-
Clotrimazole	0.21	0.03-1.45	0.054
Age	0.32	0.89-1.13	0.908
Sex			
Male	Reference	-	-
Female	0.85	0.11-6.35	0.876
Duration of denture use			
1-5	Reference	-	-
5-10	0.99	0.11-16.82	0.644
>10	0.84	0.01-15.99	0.908
Smoking	0.48	0.04-5.98	0.570
Removing denture overnight	6.56	1.12-18.11	0.023
Daily cleaning of denture			
No	Reference	-	-
Yes	1.230	0.02-12.53	0.230
Av and Ostlund classification			
Type I	Reference	-	-
Type II	0.03	0.01-0.23	0.009

OR: Odds ration; CI: Confidence interval

DISCUSSION

The results showed no significant difference in DS recovery between the two groups receiving 1% clotrimazole gel and 5% Ganoderma gel. The association of age, sex, history of denture use, denture cleaning, sleeping with denture, smoking, and Av [6] and Ostlund [7] classification with the recovery of DS was also investigated. The results indicated that only the Av [6] and Ostlund [7] classification and sleeping with denture had a significant association with DS recovery.

In other words, the percentage of complete recovery was significantly higher in patients with DS type I and patients that removed their denture overnight (before entering the study). In fact, it can be stated that removing denture overnight can be effective for relaxing the jaw and mouth and prevent the occurrence of DS or decrease its intensity as much as possible. In addition, no significant difference was observed between *G. lucidum* and clotrimazole groups. However, as the level of significance was borderline, this difference may become significant in favor of *G. lucidum* by increasing the sample size.

An in vitro study conducted by Khadka et al. [23] showed that Candida species were most sensitive to clotrimazole (82%), followed by fluconazole (64%), and then miconazole (44%). Therefore, clotrimazole was used for the control group in this study in order to have the least resistance to treatment. However, Candida susceptibility to this medication depends on the dosage of clotrimazole, and resistance to clotrimazole is still possible.

According to the present results, among the recipients of clotrimazole, which is a routine treatment for Candida, two cases were observed with no recovery after 2 weeks. Pelletier et al. [24] examined Candida isolated from the oral flora of children with AIDS and showed its resistance to clotrimazole and subsequent cross-resistance to other azoles such as itraconazole and fluconazole. Therefore, drug resistance could be one reason for no improvement in the afore-mentioned two cases.

Nayak et al. [25] conducted an in vitro study on minimum inhibitory concentration of a

toothpaste containing *G. lucidum* against *C. albicans* and showed the antifungal properties of *G. lucidum* in the form of toothpaste. In line with the findings of the current study, the minimum inhibitory concentration was 2mg/mL, which resulted in antifungal effect of *G. lucidum* in the clinical environment.

Moreover, some studies evaluated the efficacy of medicinal plants for treatment of DS. For instance, Alizadeh et al, [26] in their clinical trial showed that lesion size, type of DS, number of colonies, and patient satisfaction were not significantly different between 2% ginger mouthwash and 1000U/mL nystatin mouthwash groups. In addition, another study [16] indicated that there was no significant difference in the size of oral lesions and number of Candida colonies at 1, 7, and 14 days after the intervention between the two groups of 0.5% green tea mouthwash and 100,000U/mL nystatin suspension.

Sefidgar et al, [27] also reported complete recovery of DS and significant reduction in growth and proliferation of *Candida* colonies following the use of 1% Artemisia siberian mouthwash as compared to 500,000 IU nystatin. In an in vitro study, Jazayeri et al. [4] examined the minimum inhibitory and fungicidal concentrations of Thymus eriocalyx and Thymus kotschyanus, in comparison with nystatin against *C. albicans* growth and proliferation. In another similar study, Sholapurkar et al. [17] compared the efficacy of 2mg/mL fluconazole suspension with 1% clotrimazole oral paint in 89 patients with oral candidiasis; their oral symptoms were monitored, and microbial culture was also performed after 2 weeks. No significant difference was observed, and patients well accepted both medicines. All the above-mentioned studies pointed to the success of medicinal plants when used for over 2 weeks, which is in line with the findings of the present study on the effect of *G. lucidum* gel, as compared with clotrimazole gel, on 50 patients with DS (types I and II).

Bakhshi et al. [8] examined the effect of aqueous extract of garlic and nystatin mouthwash on 40 patients for 4 weeks. The width and length of oral lesions were measured by an oral caliper during the 4-week period. The results showed that despite a significant improvement in both groups, nystatin caused a faster recovery.

Pina et al. [28] performed microbial culture and showed that there was a 70% reduction in *Candida* colonies in the miconazole group, and a 25% reduction in the Brazilian propolis group. The reported difference was significant even though the clinical improvement was not significantly different between the two groups. Their results were consistent with the findings of the present study in terms of the obtained results and duration of treatment (14 days). Moreover, a significant association was found between the progression of DS lesions and duration of denture use in their study. However, no significant association was found between the duration of denture use and recovery in the present study.

Small sample size, complex formulation of Ganoderma used for the preparation of medicinal gel, and uncertainty about the compliance of patients at home with the diet instructions, denture use, and oral hygiene were the main limitations of this study. In addition, it has been discovered that other microbiological agents, including *Streptococcus* and *Lactobacillus* species, may accompany *C. albicans*. Thus, although nystatin is a common clinical treatment for DS, clotrimazole was chosen to be compared with Ganoderma as it has shown antibacterial as well as antifungal effects [29,30]. Nonetheless, this study was the first to use *G. lucidum* gel for treatment of DS. Therefore, further studies with a larger sample size are recommended on this gel and other therapeutic gels to assess their effects on the fungal count and obtain more robust results with higher generalizability.

CONCLUSION

The antifungal effect of *G. lucidum* on clinical recovery of patients with DS was comparable to that of clotrimazole. Thus, it is suggested for use as an alternative to clotrimazole, particularly in azole-resistant patients. However, further clinical studies are still required in this regard.

CONFLICT OF INTEREST STATEMENT

None declared.

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