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ARQUIVOS EM ODONTOLOGIA

Beneficial effects of three natural products for the treatment of denture stomatitis: a randomized clinical trial

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Aim: To evaluate the effect of three natural antifungal agents combined with routine denture care on the treatment of DS, using a quantitative mycological culture analysis.

Methods: Thirty denture wearers with denture stomatitis DS were treated using five substances: sterile distilled water (G1), nystatin oral suspension (G2), 20% alcoholic extract propolis (G3), *Punica granatum* Linné gel (G4), and Uncaria tomentosa gel (G5). The substances were used 3 times a day for 14 days. Quantitative mycological culture analysis of samples collected from the palatal mucosa was performed at three stages: before treatment (T0), after 14 days of treatment (T1), and 30 days after treatment completion (T2). Data were evaluated using Kruskal-Wallis and Friedman tests ($p < 0.05$).

Results: Palatal mucosa intragroup analysis showed a significant reduction of *Candida* CFU/mL values for all groups at T1 compared to T0 ($p < 0.05$). However, they did not present statistical differences when comparing T1 and T2 ($p > 0.05$). The intergroup analysis demonstrated that there are no statistical differences, regardless of the evaluation time ($p > 0.05$).

Conclusion: The natural products tested showed a satisfactory result on DS treatment, which proved to be equivalent to conventional topical therapy with nystatin and to treatment using only regular oral hygiene procedures.

Uniterms: Stomatitis, denture. *Candida albicans*. Biological products. Colony count. Antifungal agents.

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INTRODUCTION

Denture stomatitis (DS) is one of the most common oral pathologies, with prevalence rates ranging from 15% to 70%[1] in the world and from 19.5% to 50.6%[2] in Brazil. This condition is characterized as an erythematous and edematous mucosa, which is usually limited to the area covered by the complete denture. This condition is often associated with diabetes, immunosuppression, trauma, nutritional and metabolic deficiencies, decreased salivary flow, and mainly by *Candida* infection[1,3,4].

The recommended treatment for denture stomatitis may include topical and/or systemic antifungal therapy, oral and denture hygiene procedures, as well as denture disinfection[5-7]. However, these treatments have limitations, since therapeutic doses; the type of formulation (oral gel, buccal tablet, lacquer, and chewing gums); and the time of use of the most used drugs, such as imidazole compounds (miconazole), polyenic

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derivatives (nystatin), and amphotericin B, can have potential hepatotoxic and nephrotoxic effects, which may compromise the patient's overall health. Moreover, biofilm re-colonization and consequent reinfection of the oral mucosa is common[8-10].

Considering the high recurrence of DS and the side effects of these drugs, including diarrhea, headache, nausea, and vomiting[8], studies have focused on natural medicines that decrease adverse symptoms and have antifungal effects that are similar to allopathic drugs[11]. Reports have shown that some natural products present antimicrobial activity on oral pathogens[9-12]. Currently, *Uncaria tomentosa* (Unha de gato), *Punica granatum* Linné (Romã), and propolis are among the most studied natural medicines. Polyphenols were identified as the main organic constituents of these natural products and are mainly represented by flavonoids, phenolic acids, esters, phenolic aldehydes, and ketones, which play an important role on the development of the inflammatory process[11,13,14].

In dentistry, it has been reported that propolis can be effectively used for surgical wound healing, caries prevention, treatment of dentin hypersensitivity, treatment of aphthous ulcers, a storage medium for avulsed teeth, root canal irrigating solution, and mouthwash[15]. When evaluating medicinal plants, Herrera et al.[16] observed antimicrobial activity of *U. tomentosa* in infected root-filled teeth, while Almeida et al.[17] reported that *P. granatum* incorporated to denture adhesives played a collaborative role in *C. albicans* biofilm control. *In vitro* animal and human studies have demonstrated promising results of these natural products when evaluating their antifungal effect on strains of *Candida* spp.[16-20].

These natural products may be a useful, effective and complementary alternative for the treatment of DS. Considering the previously mentioned aspects and the lack of any clinical report in the literature, the present study evaluated the efficacy of three different natural products on DS treatment, using quantitative mycological culture analysis.

MATERIAL AND METHODS

This study was approved by the Institutional Review Board of the Bauru School of Dentistry (FOB/USP) (CAAE, 078/2010), and signed informed consent form was obtained from the participants.

DRUGS

The selection of these natural products was based on clinical and laboratory studies, when antimicrobial efficiency was proven[18,20-26]. Nystatin oral suspension (Micostatin™ 100,000 UI/mL), used as a positive control to DS treatment, and *U. tomentosa* gel (UT) (Imuno-Max gel™) were purchased at the allopathic drugstore in Bauru, Sao Paulo, Brazil. The 20% ethanol propolis extract (EP) was obtained from the Apis mellifera bee, as described by Santos et al., while the *P. granatum* L. gel (PG) was obtained as described by Vasconcelos et al. by a local pharmacy in Bauru, Sao Paulo, Brazil[18,19]. Sterile distilled water was used as a placebo. To avoid differentiation by the patients and the main researcher, all the drugs were identified with the same name (Nystatin Micostatin (100,000 IU / mL)). The entire process of placebo elaboration was done by a local pharmacy in Bauru. The tested treatments were then divided into five groups (Table 1).

Table 1 - Group distribution according to the tested substances

Groups (n = 6)	Substances
G1	Sterile distilled water
G2	Nystatin Micostatin™ (100.000 UI/mL)
G3	20% ethanol propolis extract
G4	*P. granatum* L. gel
G5	*Uncaria tomentosa* gel (Imuno-Max Gel™)

PATIENTS

Dwellers of two homeless shelters in the metropolitan region of Belem-PA, men and women, wearers of complete upper dentures, between 50 and 81 years of age, presenting a clinical diagnosis suggesting DS, were initially submitted to complete anamnesis and clinical examination by only one dentist[8]. Their dentures were visually examined to detect the biofilms. The inclusion criteria were: complete denture users with good general health and with adequate retention and support on the complete denture, and diagnosed with DS as evidenced by the clinical criteria proposed by Newton. The exclusion criteria were unstable and non-retentive dentures, in addition to the presence[8] of accentuated wear of artificial teeth, individuals with an immuno-compromised system, with non-controlled gland pathologies, users of antibiotics, people undergoing radiotherapy or chemotherapy treatment[27], and patients with DS already undergoing treatment.

A total of 37 patients with DS were assessed for eligibility; however, only 30 patients were included in this study (28 women and 2 men), according to the aforementioned exclusion criteria associated with a positive clinical diagnosis for DS based on a microbiological verification and detection of redness or erythematous points on the mucosa that come in contact with the denture acrylic resin.

The present investigation was conducted as a randomized, placebo-controlled, parallel group study and the main investigator was blinded. For that purpose, an employee from each shelter was assigned to divide the individuals into groups, as well as distribute treatments. After collecting material from the palate of each study participant, the same employees identified each sample according to the administered medication, without the knowledge of the main evaluator.

A detailed clinical examination was performed in the following regions: palate, buccal mucosa, tongue, lips, and oropharynx of each patient. Strict examination of the palate allowed for the DS classification of each patient into three clinical types, according to Newton[8].

The patients were then divided into five groups (n = 6) according to the tested treatments described in Table 1. All tested products in this research were prescribed three times a day for 14 days, which is the treatment period of denture stomatitis using conventional nystatin oral suspension. Besides the application of products, brushing of the dentures and oral mucosa with toothpaste was recommended for all patients. The medications were administered by the participants themselves or by their caregivers, and all received written guidance on the use of the products.

The tested products were applied on the mucosa and on the dentures' internal surfaces as recommended by Neppelenbroek et al.[28]. A laboratory test of the tested treatments was then performed by counting the colony forming units (CFU), which enables one to check the effect of tested substances against *Candida* spp. found on the palatal mucosa.

All 30 patients had completed their treatment within the 14-day period. Therefore, no one was excluded from the study. In addition, all patients were submitted to the follow-up evaluation after 30 days of treatment suspension.

CFU ASSAY

Samples of the erythematous areas on the palatal mucosa of each individual were collected using sterile oral swabs[28]. Each swab was inserted in a test tube containing 5 mL of 0.9% sterile saline solution and vigorously shaken for one minute. Samples of 50 uL from this suspension were placed in petri dishes containing Sabouraud agar with 5ug/mL of chloramphenicol. The petri dishes were incubated at 37°C for 48 h.

The described procedures for this assay were made in duplicate. *Candida* colony counts of each plated denture were quantified using a digital colony counter (Phoenix CP 600 Plus). The colony forming units per milliliter were determined using the drop count method. The amount of CFU mL^{-1} was calculated as the mean of duplicate samples[28]. The CFU counts were performed for all individuals before treatment (T0) and at treatment completion after 14 days (T1). One follow-up was conducted, after 30 days of treatment (T2)[29].

STATISTICAL ANALYSIS

Data were submitted to the Friedman non-parametric test for intragroup comparisons and Kruskal-Wallis test for intergroup comparisons. A significance level of 5% was considered for all tests ($p < 0.05$).

RESULTS

Quantitative microbiologic results obtained from the palatal mucosa

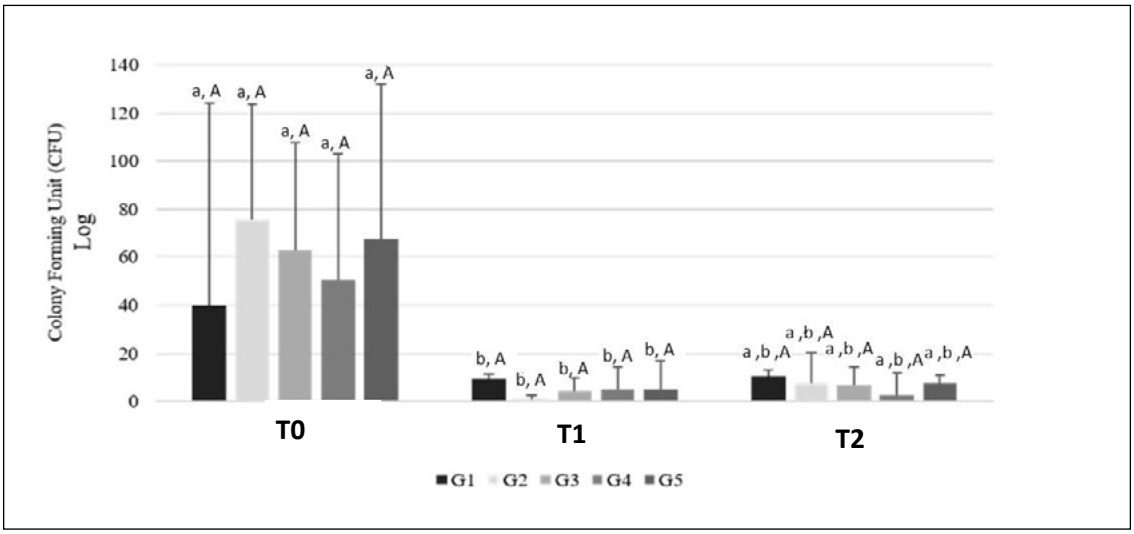
The intragroup analysis showed a significant reduction in CFU/mL values at T1, for all groups, in comparison to T0 ($p = 0.005$). Comparison between T1 and T2 showed a slight rise in CFU/mL values for T2 for all groups, except for G4, which presented a sustained fungal inhibition. However, these comparisons did not exhibit statistically significant differences within all groups ($p > 0.05$). In addition, intergroup analysis showed no statistically significant differences: T0 ($p = 0.98$), T1 ($p = 0.46$), T2 ($p = 0.88$) between all groups evaluated, regardless of the evaluation time. All medians and interquartile ranges are presented in Table 2 and Figure 1.

Table 2 - Median and interquartile range of *Candida* colony counts in CFU/mL collected from the palates during the three stages of evaluation

Groups (n = 6)	T0	T1	T2	P value †
G1	40.0 ± 84.0 ^{a,A}	9.5 ± 1.8 ^{b,A}	10.5 ± 2.5 ^{a,b,A}	0.005
G2	75.5 ± 48.0 ^{a,A}	1.0 ± 1.5 ^{b,A}	7.5 ± 12.7 ^{a,b,A}	0.009
G3	62.5 ± 45.1 ^{a,A}	4.2 ± 5.7 ^{b,A}	6.7 ± 7.6 ^{a,b,A}	0.005
G4	50.5 ± 52.3 ^{a,A}	5.2 ± 9.3 ^{b,A}	2.7 ± 9.0 ^{a,b,A}	0.01
G5	67.5 ± 64.6 ^{a,A}	5.2 ± 11.5 ^{b,A}	7.5 ± 3.5 ^{a,b,A}	0.005
P value ‡	0.98	0.46	0.88	

Horizontally, values designated with the same lowercase superscript letter were not statistically different. Vertically, values designated with the same uppercase superscript letter were not statistically different. ‡ Kruskal-Wallis test ($p = 0.05$). † Friedman test ($p = 0.05$).

Figure 1 - Median and interquartile range of *Candida* colony counts in CFU/mL, according to the performed treatment, during the three stages of evaluation. Values designated with the same lowercase letters were not statistically significant (intragroup analysis) ($p > 0.05$). Same uppercase letters designate values without statistically significant difference according to the intergroup analysis ($p > 0.05$)



DISCUSSION

C. albicans appears to be the main pathogen involved in denture stomatitis[30,31]. Different methods to treat this pathology have been proposed, such as the use of chemical solutions (sodium hypochlorite and chlorhexidine) to remove the *C. albicans* biofilm, the use of tissue conditioners to reline the prostheses, as well as the use of allopathic drugs that are applied to the

damaged areas. These drugs include polyenic derivatives (nystatin and amphotericin-B) and imidazole compounds (miconazole)[7,28,32-35]. However, these seem to have lost toxicity and resistance against *Candida* species, obtaining variable results and high recurrence rates[36].

Due to the increasing microbial resistance to these drugs and their undesirable effects, such as nausea, bad taste, low systemic uptake, diarrhea, epigastric pain, and allergic reactions[37], this study aimed to evaluate three natural products (20% Propolis alcoholic extract, *P. granatum* L. gel, and *U. tomentosa* gel), which are effective in treating DS when associated with brushing[37].

In this research, the fungicidal potential of these natural products was verified. The success occurred when the products were used three times per day for 14 days. These products significantly inhibited the fungi growth, identified by CFU/mL after swab collection from 14 and 30 days. All tested groups promoted meaningful fungi growth inhibition in this area, with a significant CFU value reduction in T1 when compared to T0 ($p < 0.05$). This is related to the fact that the products tested in this study contain bioactive principles in their composition, which give them an outstanding antimicrobial, anti-inflamatory, and anti-oxidant effects, as well as immunomodulatory properties. Among the active agents, alkaloids, tannins, and flavonoids should be highlighted, which abundantly appeared in the chemical composition of *U. tomentosa, P. granatum*, and propolis, respectively[22,38,39].

These outcomes are also in accordance with previous clinical studies[7,17,20,38,40,41]. Santos et al. demonstrated a significant regression of lesions in all patients with DS treated with 20% propolis ethanol extract and certified that these results were similar to those obtained in patients treated with nystatin[20]. In the same form, Pina et al. tested this product in older adults with DS, corroborating its fungicidal potential and demonstrating comparable results with those obtained with miconazole[38].

The antifungal potential of *U. tomentosa* has also been demonstrated. According to the present results, Tay et al. demonstrated that 2% *U. tomentosa* gel is an effective topical adjuvant treatment for denture stomatitis when used three times a day for one week[40].

Considering the recidivating characteristic of the fungal infections after the end of antifungal treatments, this study involved a 30-day assessment (T2) after the medicinal usage, period in which patients have only made the palate mucosa hygiene with toothbrush and toothpaste. As a result, a slight increase in CFU/mL from mucosa was observed in all assessed groups, except for the *P. granatum* L. group, which maintained the inhibition of fungal growth until the 30-day evaluation. Much like our results, several studies corroborate the antifungal potential of *P. granatum* L. Bassiri-Jahromi et al. carried out a study on Wistar rats infected with *C. albicans* and treated with *P. granatum* L., demonstrating promising results to treat this pathology[41]. Similarly, Almeida et al. incorporated extracts of *P. granatum* L. into denture adhesives, demonstrating an antimicrobial effect on the *C. albicans* biofilm[17].

Although the placebo group has shown the highest CFU/mL values after 14 days of DS treatment (T1), no statistical differences were found between this group and the other tested groups. Thus, the effect of brushing the palate mucosa with a toothbrush and toothpaste should be considered for this infection treatment. Therefore, the oral hygiene effect, primarily manual brushing, may possibly be optimized by the *P. granatum* L. gel action, because this was the only group that maintained the reduction of fungal growth up to 30 days (T2).

Furthermore, there are different degrees of severity of DS, and it may be necessary to use specific drugs that serve as adjuvants in the treatment of DS.

CONCLUSION

Based on the low cost, unusual side effects, and increased microbial resistance to allopathic drugs, this study showed that a 20% propolis ethanol extract, *Punica granatum* L. gel, and Uncaria tomentosa gel could be replaced by the natural products tested in this research in the treatment of DS. However, future clinical research with a greater number of patients should be performed to establish their clinical application.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Efeitos benéficos de três produtos naturais para o tratamento da estomatite protética: um ensaio clínico randomizado

Objetivo: Avaliar o efeito de três antifúngicos naturais combinados com o cuidado rotineiro com próteses dentárias no tratamento da EP, por meio de uma análise quantitativa de cultura micológica.

Métodos: Trinta usuários de próteses dentárias com EP foram tratados com cinco substâncias: água destilada estéril (G1), suspensão oral de nistatina (G2), extrato alcoólico de própolis 20% (G3), gel *Punica granatum* L. (G4) e gel *Uncaria tomentosa* (G5). As substâncias foram utilizadas 3 vezes ao dia durante 14 dias. A análise micológica quantitativa das amostras coletadas da mucosa palatina foi realizada em três etapas: antes do tratamento (T0), após 14 dias do tratamento (T1) e 30 dias após o término do tratamento (T2). Os dados foram avaliados pelos testes de Kruskal-Wallis e Friedman ($p < 0,05$).

Resultados: A análise intragrupo da mucosa palatina mostrou uma redução significativa dos valores de *Candida* UFC/mL para todos os grupos em T1 em comparação com T0 ($p < 0,05$). No entanto, não apresentaram diferenças estatísticas na comparação de T1 e T2 ($p > 0,05$). A análise intergrupos demonstrou que não há diferenças estatísticas, independentemente do tempo de avaliação ($p > 0,05$).

Conclusão: Os produtos naturais testados apresentaram resultado satisfatório no tratamento da EP, sendo equivalente à terapia tópica convencional com nistatina e ao tratamento apenas com procedimentos rotineiros de higiene bucal.

Descritores: Estomatite sob Prótese. *Candida albicans*. Produtos biológicos. Contagem de Colônia Microbiana. Antifúngicos.