Review article

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THERAPEUTIC ALTERNATIVES OF NATURAL COMPOUNDS IN TREATMENT OF CANDIDA-ASSOCIATED DENTURE STOMATITIS

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Denture stomatitis is a common inflammatory reaction affecting denture wearers, multifactorial etiology, which is usually associated with Candida species, particularly Candida albicans. The treatment of Candida-associated denture stomatitis (CADS) is difficult and complex due to its multifactorial etiology, common recurrences, as well as the lack of antifungal drug efficacy. This review aims to critically discuss several key factors affecting adhesion and biofilm formation of Candida species on acrylic surface, as well as the use of herbs, proposed as an alternative in the treatment of CADS. Many factors affect adhesion and biofilm formation of Candida spp. on acrylic surfaces, such as surface roughness of the inner surface of the prosthesis, salivary pellicle, hydrophobic and electrostatic interactions. Having in mind that denture stomatitis is a common disease in total denture wearer, that it is most common in fungal etiology and that biofilm development increases yeast resistance, application of non-synthetic, completely natural substances, such as essential oils and extracts, may be suggested as a promising alternative for treatment of CADS. *Acta Medica Medianae 2014; 53(1):73-79.*

Key words: *Candida-associated denture stomatitis, Candida albicans, essential oils, plant extracts*

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Introduction

Denture stomatitis is a common inflammatory reaction affecting denture wearers (1,2). It is manifested as inflammation and erythema of the oral mucosal areas underlying dentures, more frequent in the maxillary mucosa than in the mandibular mucosa (Figure 1) (1-4). Although etiology of denture stomatitis is multifactorial, it is usually associated with *Candida* species, particularly *Candida albicans* (*C. albicans*) (1,2). The treatment of *Candida*-associated denture stomatitis (CADS) is difficult and complex due to its multifactorial etiology, common recurrences, as well as lack of antifungal drug efficacy (2-5). The therapeutic strategy includes the use of topical and systemic antifungal drugs, chemical substances such as chlorhexidine and sodium hypochlorite, proper denture hygiene and the removal of dentures at night (3-5). The most commonly used antifungal drugs are amphotericin B, nystatin, miconazole and fluconazole. Considering the fact that the chemically used antimycotic drugs have side effect regarding toxicity, development of fungal resistance, lack of fungicidal efficacy, drug-drug interactions, high cost, alternative in using plants and their essential oils is a new trend in treatment of CADS (3,5-9).

Figure 1. Localized plane inflammation (Denture stomatitis -Type I)

This review aims to critically discuss several key factors which affect adhesion and biofilm formation of Candida species on acrylic surface, as well as the use of herbs, proposed as an alternative in the treatment of (CADS).

Candida-associated denture stomatitis (CADS)

Candida-associated denture stomatitis is affecting about 60% of the subjects carrier of a prosthesis. The major etiologic agent is *C. albicans* (5,10), although there are findings in various studies about other *Candida* species isolated from material of patients with denture stomatitis, such as *C. dubliniensis, C. parapsilosis, C. krusei, C. tropicalis* and *C. glabrata* (2,5).

C. albicans is an innocuous commensal of the microbial communities of the human oral cavity, primarily located on the posterior tongue and other oral sites as the mucosa (11,12). However, *C. albicans* may become virulent and cause candidosis in case of immunodeficiency (10). These microorganisms can stick and proliferate through the hard and soft tissues of the oral cavity, and colonize the inner denture surfaces forming a biofilm with different kinds of bacteria (5). Thus, dentures act as a reservoir for microorganisms, enabling *Candida* to re-infect the mucosal surface continually, contributing to the development of denture stomatitis (3,13).

CADS was classified according to Newton in 1962, based exclusively on clinical criteria, into three clinical types: type I is characterized by localized simple inflammation or pin-point hyperaemia. Type II, the most common type, is presented as diffuse erythema and oedema of palatal mucosal areas covered by dentures. Type III is described as granular surface or inflammatory papillary hyperplasia in central palate (1,14).

Factors which affect adhesion and biofilm formation of *Candida* species on acrylic surface

Many factors affect adhesion and biofilm formation of *Candida* on acrylic surfaces, such as surface roughness of the inner surface of the prosthesis, salivary pellicle, hydrophobic and electrostatic interactions (15).

Surface roughness directly influences initial adherence of microorganisms to surfaces, biofilm development, and *Candida* species colonization. The roughest surface of materials provides an increased chance of microorganism retention and protection from shear forces, wherein microorganisms are entrapped within surface irregularities, even during denture cleaning. Polishing of dentures provides smooth surface and thus reduce the initial adherence and accumulation of microorganisms (16).

The role of human saliva is still controversial regarding *Candida* adhesion (16). Literature finding is unclear on whether salivary pellicle on acrylic surfaces enhances or decreases initial adhesion *Candida* or even there is no effect at all (15).

The surfaces of acrylic resin are hydrophobic. Hydrophobic interaction is an important factor that affects adherence of *C. albicans* to dentures (15). However, particular *Candida* species, e.g. *C. tropicalis*, *C. glabrata* and *C. dubliniensis*, compared with *C. albicans*, show higher adherence, due to their relative surface free energy values. Another important factor which is related to the development of CADS is surface free energy (16). According to *C. albicans* adherence, it has been found that higher surface free energy of the resin will influence an increase in adherence of *C. albicans*, while more hydrophobic surface is expected to cause less cell adherence (16).

The adherence of *Candida* to polymers can also be influenced by electrostatic interaction (17). Yeasts whose surfaces have a positive charge are more adherent due to repulsive forces between negatively charged yeast cell and polymer surfaces (5).

Candida biofilm development

Biofilms are microbial communities enclosed in a matrix of extracellular polymeric substances, showing different phenotypic features in regard to their planktonic or free-floating counterparts (18).

C. albicans biofilm development progresses in three distinct developmental phases:

Phase I is an early stage and occurs within 1-11 hours. *Candida* cells adhere to a substrate or surface within two hours, because of non-specific interactions such as hydrophobic and electrostatic forces between the cells and the substratum, and the *C. albicans* cells are blastospores. In addition, glycoproteins are expressed to facilitate stronger adhesion. Microcolonies appear at 3 to 4 hours, and after 11 hours; aggregations of *C. albicans* appear on substratum irregularities.

Phase II is intermediate/developmental stage and occurs within 12-30 hours. The *Candida* biofilm community can be seen as a bilayer composed of yeasts, germ tubes and young hyphae with a matrix of extracellular polymeric substances (EPS). EPS encapsulation matrix contains polysaccharides produced by the microbial components which are often located in a state of reduced metabolic activity, therefore the biofilm has a non-cellular layer or EPS covering the fungal microcolonies.

Phase III is the last stage and represents the maturation which appears within 38-72 hours. Extracellular material enlarges with incubation time, while *C. albicans* yeasts, pseudohyphae and hyphae are fully embedded in a matrix (7).

Biofilm development increase drug resistance wherein resistance comes quickly after *C. albicans* substrate adherence (19,20). There is a variety of reasons which could explain increased antimicrobial resistance of microorganisms in biofilms which are surrounded by an extracellular matrix, which makes protection from environment and which could slow antifungal drug penetration. Phenotypic changes which are the result of limited availability of nutrients and oxygen in biofilm containing yeasts and a non-growing bacteria cause less susceptibility of microbes to antimicrobial drugs (19-22). Chandra et al. have found that antifungal drug resistance of amphotericin B, nystatin, fluconazole and chlorhexidine increases during biofilm development, so that *C. albicans* cells were highly resistant, by 72h in mature biofilms (6).

Therapeutic alternatives among essential oils and herbal extracts

Natural products express antibacterial and antifungal activities as well as anti-inflammatory and antioxidant effects, and it has been proven that they are the alternative substitution of chemical substances with less adverse effects on humans (3,9). A wide variety of the plants extracts and essential oils have been traditionally used as antifungal agents against *C. albicans*, therefore their role in treatment of *Candida*-associated denture stomatitis might be of certain importance (3).

In a biweekly, double-blind randomized clinical trial, patients with complete upper denture were medicated with a gel containing essential oil of *Pelargonium graveolens* L. in order to treat denture stomatitis caused by *C. albicans*. Administration of 1% oil of *P. graveolens* in the form of the gel in the case group was more efficient in reduction of fungal growth than control group. Considering mycological culture data and clinical examination before and after treatment, 34% of patients in the case group recovered completely and 56% of them reported partial improvement. It has also been reported that the gel containing the essential oil of *P. graveolens* dramatically reduced erythema in patients from case group (23).

The same authors monitored the effectiveness of *Satureja hortensis* L. essential oil in the complete denture wearers, as well. The double-blind clinical trial included the two-week use of a gel containing 1% of *S. hortensis* essential oil. Participants from the case group had a statistically significant improvement in count of *C. albicans* colony and the reduction of the erythema of palatal mucosa compared with control group (87.5% with regard to 30%, respectively) (8). The essential oil of *S. hortensis* is reputed to have a wide antimicrobial spectrum, including the inhibition of the growth of the human bacteria, fungi and yeasts (24,25). The main compound in the essential oil of this plant is monoterpene carvacrol (26). Carvacrol, oxygenated monoterpen, is considered to have responsibility for the antifungal effect of the oil which seems to be related to the inhibition of ergosterol biosynthesis (2). Other natural compounds from essential oils eugenol, farnesol, geraniol, linalool, menthol, menthone, terpinen-4-ol, α-terpineol and tyrosol, along with carvacrol, expressed strong antifungal *in vitro* activity, as well. The investigation implied oral *Candida* isolates from denture wearers whereby minimal inhibitory concentrations of compounds ranged from 0.03% to 8%. (2). Linalool, terpinen-4-ol, geraniol and eugenol were the most effective against *C. albicans* while carvacrol was active aginst *C. glabrata* and *C. tropicalis,* as well (2). Carvacrol manifested a powerful activity against *Candida spp*. even against fluconazole-resistant isolates (28,29). Besides carvacrol, *in vitro* anti-*Candida* activities at low concentrations were exhibited by geraniol, linalool, menthol, terpinen-4–ol, α-terpineol and eugenol against fluconazole-resistant *C. krusei* and *C. glabrata* (27).

Zataria multiflora Boiss. has shown the beneficial effect to the treatment of CADS. The open, randomized, controlled, clinical study assessed the difference in efficiency of 2% gel containing miconazole and 0.1% gel containing essential oil of *Z. multiflora* which were administered four times daily for 2 weeks. Both preparations were able to significantly reduce the erythema surface and decrease the colony count of the palatal mucosa. Miconazole was more potent in reducing the number of denture colonies, but essential oil of *Z. multiflora* alleviated the erythema of the palate more efficiently than miconazole gel. It is considered that the main components, thymol, carvacrol, *p*-cymene, linalool and γ-terpinen were responsible for such activities of the oil (30).

Natural products which are known on the basis of their folklore usage could be the effective agents for the treatment of denture stomatitis. Garlic has a number of physiological effects with lack of side effects, so it could be a suitable substitution for nystatin in healing of oral candidosis, particularly related to denture stomatitis. In a randomized, double-blind clinical trial, Bakhshi et al. compared garlic aqueous solution with nystatin mouthwash in the patients with denture candidosis. After four weeks of oral application of nystatin suspension or garlic aqueous solution, three times a day, researchers noticed that the changes in the length and width of erythema were significantly ameliorated in both treatment groups. A more rapid recovery was demonstrated in participants who used nystatin, but both groups resulted in significant recovery (31).

Pinelli et al. investigated the treatment of denture stomatitis in institution and compared its activity with nystatin and miconazole. Patients used miconazole oral gel, nystatin drops or *R. communis* oil, for 30 days of treatment. It was interesting that neither group showed a statistically significant suppression in the numbers of yeasts cells at any time. However, miconazole and *R. communis* oil were able to improve the clinical presentation of stomatitis in patients, with statistical significance (32). A weak effect of nystatin might be attributed to resistance of *C. albicans,* which has been constantly increasing, and the low adherence of elderly to the treatment (33). Mordenti et al. claimed that sodium ricinoleate from castor oil polymer may change the formation of biofilm by decreasing its acidity (34). Another possible mechanism against fungi may be the influence to the chitin, a long-chain polymer of N-acetylglucosamine, the main component of the cell walls of *C. albicans* (35).

Punica granatum L. fruit extract could be effective topical antifungal agent for the treatment of *Candida* associated denture stomatitis. In a clinical trial, patients used 2% miconazole or 1.25% *P. granatum* extracts gels three times a day topically, for two weeks. All patients from the study reported the improvement of symptoms or total recovery of lesions. The outcome of the study was that applied gels achieved regular and satisfactory clinical response as well as the laboratorial negativity of yeasts. Tannins and polyphenols are the major compounds of the extract of the fruits of *P. granatum* and considered to be responsible for the effect. Tannins may affect the cell membrane of the yeasts due to precipitation of proteins, however, the specific mechanism of action against *Candida* is not well studied (36).

In addition to *in vivo* studies, there is a number of *in vitro* studies examining the inhibition of adhesion of the *C. albicans* cells to the surface of acrylates by the natural antifungal agents.

Sookto et al. found that essential oil of *Salvia officinalis* L. manifested strong anticandidal activity and expressed inhibitory effects on the adhesion of the *C. albicans* to polymethyl methacrylate resin surface. It was established that immersion of acrylate in the essential oil at concentrations of 2.780 g/l, 1.390 g/l and 0.695 g/l, at room temperature for 30 min, significantly decreased the adhesion of *C. albicans* strains to polymethyl methacrylate resin surface, compared to distilled water (37). The major compounds which are considered to be responsible for antimicrobial activity are oxygenated hydrocarbons, monoterpene and sesquinterpene hydrocarbons particularly 1,8-cineole, *α-β*-thujone and borneol (38).

A leaf ethanolic extract of *Streblus asper* Lour. manifested strong activity in suppressing *C. albicans* adhesion to acrylic in the *in vitro* study. The minimum concentration of the extract able to significantly reduce the *Candida*-adherence after a 4h exposure was 31.25 mg/ml. The concentration of 62.5 mg/ml of the extract caused a significant reduction of *Candida* adhesion to acrylic and occurred after 1 min of exposure. Researchers also conducted a pre-treatment of yeast with 62.5 mg/ml of the extract for 1h, before adhesion test, and reported significant suppressing of the adherence, 20.54%, compared to the untreated control (39). *S. asper* can inhibit the germination of *C. albicans,* thus the extract, probably, interferes in changes of cell surface hydrophobicity, and consequently reduces *Candida* adhesion (40).

A pretreatment of acrylic surface with ethanolic extract of *Boesenbergia pandurata* (Roxb.) Schltr. rhizome resulted in significantly reduced adhesion of *C. albicans* to denture acrylic surface. The pretreatment implied immersing of acrylic in solution of the extract at concentrations of 25, 50 and 100 mg/ml and then inoculation with *C. albicans*. The greatest inhibition of adherent yeasts cells was recorded at 100 mg/ml and was approximately 75% (41). The effects of *B. pandurata* extract are visible mostly due to changes in cell surface of the yeasts, interacting with the production of extracellular matrix or a fibrillar floccular layer and modulating of the surface hydrophobicity. It is also possible that *B. pandurata* extract decreases the adhesion of yeasts to acrylic surfaces by blocking adhesins on the surface of the cell (42).

An ethanolic extract of fruits from *Phyllanthus emblica* L. was also investigated by the same Thailand investigators. In the study they monitored the efficacy of the extract to prevent the attachment of *C. albicans* to denture acrylic surfaces. The inhibition of adhesion was achieved at concentrations of 75-300 mg/ml of the extract reducing 36%-80% of the yeasts cells (43). Geraniin, quercetin 3-*β*-D-glucopyranoside, kaempferol 3-*β*-D-glucopyranoside, isocorilagin, quercetin and kaempferol present in *P. emblica* may affect the cell surface structures or integrity and could mask the adhesions on the yeast or on the receptors (44).

A polymethyl methacrylate based tissue conditioner incorporated with origanum oil exhibited a strong resistance to the *Candida*-adhesion without influence on the physical properties of the material. Sixty vol% origanum oil in tissue conditioner significantly reduced the number of yeast cells, 16±1.15 cells/mm^2 at 1 day and 32±4.00 cells/mm^2 at 1 week, in comparison to control, 90±6.80 cells/mm^2 at 1 day and 165 ±7.63 cells/mm^2 at 1 week. The oil's antimicrobial effect was found to be based on the inhibition of germination and filament formation of a microbe, thanks to carvacrol and thymol (45).

Baicalein is a flavonoid, a major component of *Scutellaria baicalensis* Georgi, which was examined for its preventive anti *Candida*-adhesive and antifungal properties. Confocal laser scanning microscopy indicated that over 70% inhibition of *C. albicans* biofilms was achieved with dimethyl sulfoxide solution of baicalein at concentrations ranged from 4 µg/ml to 32 µg/ml. The water–hydrocarbon two-phase test showed a decrease in hydrophobicity of yeasts cell surface when treated with baicalein, which was the result of inhibition of biofilm forming (46).

The hydrophobicity of *C. albicans* cell surface could be changed by *Azadirachta indica*

A. Juss. aqueous extract made of leaves, as well. The concentration of 0.01 g/ml of *A. indica* extract managed to increase the hydrophobicity and consequently reduce the capacity of cells to adhere to composit resin. On the other hand, the extract was unable to inhibit the growth of *C. albicans* cells, probably due to low concentration of bioactive compounds extracted with water, which may be increased with an alcohol as extracting agent (47).

An *in vitro* study examined the effects of well-known antifugal natural product *Melaleuca alternifolia* (Maiden & Betche) Cheel essential oil on the inhibition of *C. albicans* when mixed with tissue conditioners. The mixture of Coe-Comfort or Fitt conditioners with 1 ml of 20% *M. alternifolia* oil demonstrated a strong and rapid inhibitory and fungicidal activity of *C. albicans*. In *in vivo* study, patients with Coe-Comfort dentures with 1 ml of incorporated essential oil reported a significant decrease in palatal inflammation which was almost the same as in patients receiving nystatin. A high significant inhibition in *C. albicans* growth was found in group with denture containing essential oil, compared to nystatin and control group (48).

Conclusion

Having in mind that denture stomatitis is a common disease in total denture wearer, and that it is most commonly of fungal etiology, application of non-synthetic, completely natural substances, such as essential oils and extracts, may be suggested as promising alternative for treatment of CADS. However, further works and clinical studies are recommended before their usage. It is important to use standardized, scientifically studied plant medications due to the fact that not all herbs are safe and nontoxic.

Considering the increasing resistance of the fungi against antifungal agents, formation of *Candida* biofilm, and generally positive attitude of patients for herbal treatment, natural products could be the alternative substitutions of chemical substances with less adverse effects on humans, which is relevant for effective treatment of *Candida* infections.

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PRIRODNA JEDINJENJA U TERAPIJI PROTEZNOG STOMATITISA IZAZVANOG GLJIVAMA RODA CANDIDA

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Protezni stomatitis je veoma čest inflamatorni proces kod nosilaca mobilnih zubnih proteza, multifaktorijalne etiologije. Najčešće se dovodi u vezu sa gljivama roda Candida, pri čemu je Candida albicans glavni uzročnik. Tretman proteznog stomatitisa izazvanog kandidom je težak i kompleksan zbog multifaktorijalne etiologije, čestih recidiva i rezistencije mikroorganizama na antifungalne lekove. Cilj ovog rada bio je istaći najbitnije faktore koji utiču na adherenciju gljivama roda Candida za akrilat i da razmotri upotrebu lekovitog bilja kao alternative u terapiji proteznog stomatitisa izazvanog Candida spp. Mnogi faktori utiču na adheziju i formiranje biofilma Candida spp. na površini akrilata, kao što su hrapavost površine unutrašnje strane proteze, salivarna pelikula, hidrofobnost i elektrostatske interakcije. Imajući u vidu činjenicu da je protezni stomatitis često oboljenje kod onih koji nose totalne zubne proteze, da je najčešće gljivične etiologije, da razvoj biofilma povećava rezistentnost na lekove, primena nesintetičkih sredstava, potpuno prirodnih, kao što su etarska ulja i ekstrakti, mogu biti dobra alternativa u tretmanu proteznog stomatitisa izazvanog kandidom. *Acta Medica Medianae 2014;53(1):73-79.*

Ključne reči: *protezni stomatitis, Candida albicans, esencijalna ulja, biljni ekstrakti*