INTRODUCTION

As early as in the ancient times, a relationship between the condition of the teeth and diseases of other organs was noted. Nowadays, it is beyond any doubts that there is an association between a poor condition of the oral cavity and occurrence of many systemic diseases, such as sinusitis, renal inflammation, heart diseases, joint pains, and consequences of neglected oral inflammation are treated not only by dentists, but also by other medical specialists. Therefore, the condition of teeth and gums as well as various pathological conditions in the oral cavity or pharynx (e.g. tonsils) have a fundamental influence on the condition of the entire body [1, 2].

Patients often inadequately maintain oral hygiene and seek advice only when they have developed inflammation. Lesions in the oral cavity deteriorate the patients’ quality of life. Most often, they are primary lesions, such as papules, vesicles, blisters, abrasions and secondary lesions such as ulcerations, erosions, cracks or scars. These changes are accompanied by burning pain, dryness and discomfort of varying degrees, often unpleasant mouth odour (halitosis), or bleeding. Epidemiological studies indicate that the most common diseases include: mycoses, dermatoses (lichen planus, pemphigus), affecting the oral mucosa, precancerous conditions and cancer of the oral cavity, burning mouth syndrome, aphthoses, tongue diseases, post-traumatic changes, allergic inflammation of the oral cavity, and lesions of highly probable allergic aetiology [3, 4].

In dentistry, apart from well-known synthetic substances, such as chlorhexidine, choline salicylate or octenidine there are also herbal preparations, based on plant extracts, essential oils or their components [5, 6]. They are used for care, hygiene and treatment of diseases of the oral and pharyngeal mucosa. Positive monographs of the European Committee on Herbal Medicinal Products (HMPC) have been published on plant materials such as chamomile capitulum, calendula flower, sage leaf or oak bark.

EFFECTIVENESS OF COMPOSED HERBAL EXTRACT IN THE TREATMENT OF GINGIVITIS AND ORAL AND PHARYNGEAL MUCOSA – REVIEW OF STUDIES

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ABSTRACT

Intensive studies on properties of synthetic compounds are simultaneously conducted with studies on the effectiveness and safety of drugs derived from natural compounds. These drugs have been effectively used for years in dentistry, in treatment of inflammatory conditions of the oral cavity and in laryngology, in treatment of pharyngeal inflammatory conditions. The subject of this article is a compilation of studies conducted on medicinal products containing composed ethanolic extract as an active substance, and obtained from: chamomile capitulum (Matricaria recutita L.), oak bark (Quercus spp.), sage leaf (Salvia officinalis L.), arnica herb (Arnica spp.), calamus rhizome (Acorus calamus L.), peppermint herb (Mentha piperita L.), thyme herb (Thymus spp.) Preclinical studies confirmed that a particular tested plant extract exhibits antimicrobial (antibacterial, antifungal and antiprotozoal) as well as anti-inflammatory, immunomodulatory and astringent properties. Under clinical conditions, it was confirmed that drugs containing the analysed extract used in periodontology, in prevention and complex treatment of gingivitis, periodontitis as well as diseases of oral mucosa (but also the throat) of viral, bacterial, fungal and protozoal aetiology significantly improved the effectiveness of therapy, shortened the treatment and improved the patients’ quality of life. The above preparations used in dental surgery contributed to faster tissue regeneration, more quickly relieved pain and swelling after a surgery or difficult dentition. Furthermore, drugs containing the above-mentioned extract can also be successfully used for oral cavity decontamination in the case of various diseases of teeth or the oral and pharyngeal mucosa. The tested composed herbal extract (CHE), applied in the form of a mouthwash and in the form for topical application with benzocaine content (CHEB), is a component of drugs which are great alternatives to widely used synthetic drugs. They are characterised with high effectiveness, comparable to that of synthetic agents, and a higher safety profile. Results of pharmacological and clinical studies justify their use in both prevention and treatment of inflammatory diseases of the gums, periodontium, oral cavity and pharynx.

KEY WORDS: periodontology, gingivitis, periodontitis, oral mucositis, dental surgery, herbal extract, Dentosept, Stomatofit
Chamomile flower extract is one of the most common plant-based components used in mouthwashes. Due to its essential oil (rich in chamazulene, alpha-bisabolol) and flavonoids (apigenin and luteolin), it exhibits antioxidant, antibacterial, anti-inflammatory, anti-fungal, and anti-inflammatory properties, which inhibit neoplastic angiogenesis [7-10].

The second, equally popular component of herbal medicines used in dentistry is sage leaf. Essential oil, isolated camphor, flavonoids, catechin tannins and carnosol, being active compounds of sage leaves, have disinfectant, bactericidal and fungicidal (mostly against Candida) [11-13], antiviral [14], anti-inflammatory, astringent and tanning properties [12,15].

Other frequently used plant materials include: arnica leaf or flower, thyme herb, peppermint herb, calamus rhizome or oak bark. Arnica herb has anti-inflammatory effects due to its sesquiterpene lactones which inhibit cyclooxygenase activity [16]. Essential oil and phenolic acids, found in arnica herb, exhibit antimicrobial properties against Gram-positive and Gram-negative bacteria [16,17]. Arnica herb reduces swelling, promotes granulation and improves local blood circulation [16]. Thymol contained in thyme herb (a component of thyme oil), shows strong antibacterial [18] and antifungal activity [19,20] and phenol acids, apart from having a strong antiseptic and local anaesthetic effect on mucosa, also reduce congestion [11].

Peppermint extract and oil are also characterised with antibacterial [21,22] and antifungal [20,21], but also antiviral, antioxidant, anti-inflammatory [22] and immunomodulatory properties [21]. Extract from calamus rhizome also shows an antibacterial and antifungal effect [23]. Tannins of oak bark and calamus rhizome have strong astringent, bactericidal and anti-inflammatory properties [24]. Tannins contained in oak bark form stable and insoluble complexes with proteins of microorganisms. Hence, they possess bactericidal properties. Besides, through their influence on capillaries, they minimize vascular permeability and microbleeding [11].

Herbal medicines are usually available in the form of mouthwashes but also gels, ointments, lotions or sprays.

THE AIM

The aim of this review is to summarize available non-clinical and clinical studies conducted for a unique herbal composition, in the form of composed ethanolic extract obtained from: chamomile capitulum (Matricaria recutita L.), oak bark (Quercus spp.), sage leaf (Salvia officinalis L.), arnica herb (Arnica spp.), calamus rhizome (Acorus calamus L.), peppermint herb (Mentha piperita L.), thyme herb (Thymus spp.). This extract is included in original herbal medicinal products which are available under the following trade names: Dentosept (Poland and Lithuania), Stomatofit (Russia, Ukraine) and the above-mentioned extract + substance with topical anaesthetic effect – benzocaine, under the names: Dentosept A (Poland) and Stomatofit A (Russia, Ukraine).

MATERIALS AND METHODS

This literature review was made by searching the PubMed database using key words – names of individual products. Additional data were sought in the Google search engine by entering key words: “product name+research+pdf” in the Polish, English, Russian and Ukrainian language versions. The data are presented on the basis of the collected materials and own materials of the responsible entity (Phytopharm Klęka SA, Poland).

REVIEW AND DISCUSSION

COMPOSED HERBAL EXTRACT AS AN ACTIVE SUBSTANCE OF HERBAL DRUGS

As it has been mentioned, Dentosept and Stomatofit preparations, which are available in the form of concentrate for oral cavity rinsing solution and Dentosept A and Stomatofit A, which are available in the form of ready-to-use thick liquid for direct application onto the oral cavity mucosa, contain liquid extract composed of seven medicinal plants: chamomile capitulum, arnica herb, sage leaves, oak bark, thyme herb, peppermint herb and calamus rhizome (CHE). Besides, Dentosept (Stomatofit) A contains a substance which has a topical anaesthetic effect, i.e. 2% benzocaine and also hydroxyethylcellulose and glycerine, which increase viscosity and adhesion to the mucous membrane (CHEB).

Dentosept can be used as an anti-inflammatory, antibacterial, disinfectant and astringent agent: in inflammations of the mucosa of the oral cavity and pharynx, gingivitis and stomatitis (including glossitis), superficial periodontitis, susceptibility to gingival bleeding and auxiliarily in periodontopathies [25]. Dentosept A is also recommended for aphthae and oral cavity sores (denture-related) due to its topical anelgesic effect and adhesion to the application site [26]. A drug containing CHE was for the first time authorised for marketing in Poland in the year 1987, whereas the one containing CHEB – in 1992.

PHARMACODYNAMIC PROPERTIES OF CHE AND CHEB

ANTIBACTERIAL, ANTIFUNGAL AND ANTIPROTOZOA PROPERTIES

A lot of studies have been conducted on antibacterial, antifungal and antiprotozoal properties of CHE and CHEB. Both the product versions showed a potent bactericidal or bacteriostatic activity against Gram-positive and Gram-negative bacteria, [27-29] as well as fungi [27, 30-32] and protozoa [33]. Table 1 includes a list of studies and susceptible strains. Medicinal products containing CHE can be used auxiliarily both in prophylaxis and therapy of infections in the oral and pharyngeal cavity, of bacterial, fungal (including yeast) or protozoan etiology. Studies revealed that their efficacy is comparable to or higher than that of standard synthetic agents, e.g. chlorhexidine or octenidine. A compilation of studies on chlorhexidine and 12 mouthwashes with, among others, antifungal activity (Azulan, Colgate Plax Complete Care Sensitive, Corsodyl 0.2%, Curasept ADS 205, Dentosept, Dentosept A, Eludril Classic, Listerine Total care, Octenidol, Oral-B Pro-Expert Clinic Line, Sylveco and Tinctura salvia) revealed that CHE showed a stronger antifungal effect and affected a broader spectrum of fungi than chlorhexidine, which is considered to be a gold standard for rinsing the mouth [30].


**ANTI-INFLAMMATORY AND IMMUNOSTIMULATING EFFECTS**

CHE, due to the content of extracts from oak bark, sage, peppermint and chamomile flowers, effectively inhibits inflammatory processes and enhances regeneration of the mucous membrane of the oral cavity [8, 12, 16, 17, 23]. Presumably, the anti-inflammatory effect of the extract is associated with the presence of flavonoids. It has been shown that the anti-inflammatory mechanism of action of flavonoids is related to inhibition of enzymes producing eicosanoids, in particular, phospholipase A2, cyclooxygenase and lipoxygenase. This leads to a decrease in the concentration of prostanooids and leukotrienes. Another mechanism of action involves inhibition of histamine release, phosphodiesterase, protein kinases and transcriptase activation [34]. The anti-inflammatory effect has also been clinically proven [35]. Immunomodulatory effects of CHE have also been demonstrated. The drug administered in a wide range of concentrations (0.006-0.15%) affected the activation of T lymphocytes [36].

**ASTRINGENT ACTION**

Tannins, contained in plants such as oak bark, sage leaf, calendula rhizome, are mainly responsible for the astringent effect of CHE. They cause coagulation of proteins, which leads to a formation of a protective barrier on the surface of the mucous membrane. This barrier protects against an influence of harmful and irritating factors, thereby facilitating tissue regeneration. Besides, tannins show anti-inflammatory and anaesthetic effects [23, 24, 37].

**APPLICATION OF CHE AND CHEB IN PERIODONTICS – RESULTS OF CLINICAL STUDIES**

**TREATMENT OF GINGIVITIS AND PERIODONTITIS**

The main cause of gingival and periodontal inflammation is plaque, a bacterial biofilm that, when removed irregularly and improperly, makes up a reservoir for bacteria [38]. Inadequate oral hygiene, systemic diseases, traumas, and an improper diet contribute to the development of infection. Untreated gingivitis leads to a periodontal disease, which often becomes chronic and leads to bone destruction of the alveolar process and subsequent tooth loss. While gingivitis is reversible condition, periodontitis leads to irreversible changes in all its components. However, an appropriate therapy can effectively inhibit development of the inflammatory process [39]. Professional teeth cleaning is a basic therapeutic and prophylactic procedure, applied in patients with periodontal disease. Nevertheless, in many clinical cases, it is insufficient and it should be accompanied by pharmacotherapy.

Synthetic or herbal drugs may be administered. Table 2 provides a summary of clinical studies, conducted for the active substances CHE and CHEB, together with a presentation of results. The conducted studies confirm the effectiveness of the tested extract in supporting mechanotherapy and as a part of comprehensive treatment.

Both CHE and CHEB containing medicinal products were well tolerated and did not experience any discomfort [42]. Besides, patients enjoyed the pleasant flavour of the preparation, changes accompanied by positive dynamics of periodontal indices. Similarly in another 14-day study, CHE significantly improved the condition of patients with diagnosed periodontal inflammatory diseases (i.e. gingivitis and chronic periodontitis). Inflammatory indices and gingival bleeding got improved. Visual signs of inflammation in the area of the free gingival margin also disappeared, i.e. the gingiva was pale pink in colour and closely adhered to the tooth cervix [36].

The tested preparations, containing CHE and CHEB, also showed antibacterial and anti-inflammatory effects in the comprehensive treatment of inflammatory periodontal diseases and they entirely restored hygienic conditions in the oral cavity and reduced bleeding. Both the preparations reduced pain. However CHEB, containing benzocaine, which has anaesthetic properties, appeared to be more effective in reducing pain. The efficacy of both preparations was comparable with regards to improving the dynamics of the main clinical symptoms of inflammatory periodontal disease. Thus, it can be concluded that both CHE-containing drugs demonstrate a clear therapeutic effect in comprehensive treatment and prevention of inflammatory periodontal disease and are well tolerated (no adverse effects were reported) [40].

The effect of applying a CHE-containing product on the clinical periodontal status and the activity of exoglycosidases (N-acetyl-β-hexosaminidase – HEX and β-glucuronidase – βG) in the periodontal pocket fluid in patients with chronic periodontitis, after a professional tooth cleaning procedure, was also studied. The study group additionally used a plant preparation after the mechanotherapy procedure, while the control group underwent only the cleaning procedure. Mechanotherapy was shown to have a beneficial effect on the periodontal status, as a decrease in the HEX and βG activity was noted in both groups, and administration of a mouthwash in this case did not improve periodontal indices and did not reduce enzymatic activity [41].

The authors also evaluated the efficacy of application of CHE in the treatment of chronic catarrhal gingivitis in adolescents (15 – 19 years), whose oral hygiene was unsatisfactory, which was considered to be a major cause of complaint. The application of the preparation in the study group significantly reduced congestion and swelling of gingival tissues and stopped bleeding [38].

Similar results were obtained by the researchers regarding the treatment of adult patients with chronic catarrhal gingivitis, manifested by gingival bleeding, exacerbated by brushing teeth and eating hard food. It has been shown that the inclusion of a CHE-containing drug in the primary treatment regimen of generalized periodontitis promotes earlier and stable periodontal tissue changes accompanied by positive dynamics of periodontal indices. Besides, patients enjoyed the pleasant flavour of the preparation, tolerated it well and did not experience any discomfort [42].

The effectiveness of the drug in the form of a mouthwash was also studied in treatment of gingival inflammation in intellectually disabled children, aged 7–16 years. Patients...
Table 1. Summary of antimicrobial trials

<table>
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<tr>
<th>Source</th>
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<th>Data and Results</th>
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| Kędzia A, 2000 [27] | The effect of Dentosept on anaerobic bacteria isolated from gingival pockets | 1. 186 strains of anaerobic bacteria, isolated from 24 patients with periodontitis, were tested.  
2. Dentosept showed high activity against all tested anaerobic microbes  
3. The most sensitive (MIC≤0.6mg/ml) strains included: Bacteroides, Porphyromonas, Peptostreptococcus, Propionibacterium  
4. Prevotella and Fusobacterium were less sensitive  
5. Peptococcus, Clostridium and Veillonella were much less susceptible (MIC 5 – ≥20 mg/ml) |
| Kędzia A, 2006 [28] | The activity of Dentosept A against anaerobic bacteria isolated from oral cavity infections | 1. 118 strains of anaerobic bacteria isolated from 21 patients with infections of oral cavity were tested  
2. Dentosept A showed high activity against all tested anaerobic microbes  
3. Prevotella and Porphyromonas were most sensitive (MIC in ranges =0.6 – 1.2 mg/ml)  
4. Fusobacterium and Bacteroides were less sensitive (MIC=0.6 – 1.2 mg/ml)  
5. Eubacterium (MIC=0.6 mg/ml) and Micromonas (MIC =0.6 – 2.5 mg/ml) were most of Gram-positive anaerobic bacteria  
6. Veillonella spp. (MIC ranges 5.0- ≥20.0 mg/ml) were much less susceptible |
| Sender-Janeczek A, Kędzia A, Kwiatowska M, Ziętek M [29] | Antimicrobial efficacy of Dentosept and 0.1% chlorhexidine gluconate on anaerobic bacteria | 1. Anaerobic bacteria were isolated from 24 patients with advanced chronic periodontitis or gingivitis or mucosal ulceration  
2. After 15 min. Dentosept acted in a bactericidal manner (MBS) against 60% strains of anaerobic bacteria and after 30 min. – against 100% of these strains, whereas 0.1% solution of chlorhexidine gluconate demonstrated bactericidal activity (MBC) against all strains of anaerobic bacteria as early as after 15 min.  
3. Dentosept inhibited the growth of all anaerobic germs in concentration ranges ≤ 0.8 to ≥ 25.0 mg/ml and chlorhexidine gluconate in concentrations ranging from ≤ 0.007 to 0.062 mg/ml |
| Moroz J, Kurnatowski P [30] | In vitro effect of selected mouthwashes on standard fungal strains | 1. 8 reference fungal strains were investigated: C. albicans x3, C. dubliniensis, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis  
2. 13 mouthwashes were used in the study: Azulan, Colgate Plax Complete Care Sensitive, Corsodyl 0.2%, Curasept ADS 205, Dentosept, Dentosept A, Eludril Classic, Listerine Total Care, Octenidol, Oral-B Pro-Expert Clinic Line, Sylveco and Tinctura salviae and pure Chlorhexidine in concentration 0.125%; 0.25%, 0.5% and 1%  
3. The largest inhibition zones were produced by Dentosept, Chlorhexidine and Colgate  
4. The smallest inhibition zones were produced by Octenidol  
5. A statistically significant difference (p<0.05) in the growth inhibition diameter was found for various species of fungus in the reference group: without dilution and with 0.5 dilution of Chlorhexidine, Colgate, Corsodyl, Octenidol, Oral-B and Sylveco, and for all dilutions of Dentosept A  
6. The lowest MIC values, indicating the strongest potential activity, were obtained for Dentosept A, followed by chlorhexidine  
7. The highest MIC values, indicating the lowest activity, was calculated for Curasept and Octenidol |
| Radwan-Oczko M, Kędzia A, Michalak A [31] | The activity of Dentosept A against yeast-like fungi | 1. The studies focused on 30 strains of yeast-like fungi, including Candida (26 strains), Geotrichum (2), Rhodotorula (1) and Saccharomyces (1), which were isolated from infections, apart from 6 strains from model species: Candida albicans – x2, Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis  
2. After 15 minutes of exposure to the preparation, 81% of fungal strains were eliminated, and after 30 minutes, all tested strains from Candida type were eliminated and a fungicidal activity (MFC) towards Geotrichum candidum, Rhodotorula mucilaginosa and Saccharomyces cerevisiae strains was observed as early as after 15 minutes |
2. Dentosept was the most active towards Candida mesenterica and C.parapsilosis (MIC≤5.0 mg/ml) and the least active towards C. dubliniensis, C. guilliermondii and C. krusei (MIC 15.0 – ≥ 20.0 mg/ml) |
The in vitro activity of selected mouthwashes on the reference strains of Trichomonas tenax and Entamoeba gingivalis

1.14 agents used as mouthwashes were tested, with two pure compounds acting as mouthwash ingredients, i.e. 20% benzocaine and 0.2% chlorhexidine, as well as 12 commercially available formulas: Azulan, Colgate Plax Complete Care Sensitive, Corsodyl 0.2%, Curasept ADS 205, Dentosept, Dentosopet A, Eludril Classic, Listerine Total Care, Ocentodol, Oral-B Pro-Expert Clinic Line, Syveco and Tinctura salviae.

2. All undiluted mouthwashes, tested in this work, exhibited a lethal impact on both Entamoeba gingivalis and Trichomonas tenax after 1, 10 and 30 minutes, respectively.

3. All undiluted mouthwashes, tested in this work, exhibited a lethal impact on both protozoa; for both of them, the strongest effect was seen for Dentosept A.

Clinical and laboratory justification for topical application of the herbal preparations Stomatofit and Stomatofit A in complex diseases of the oral mucosa

1. Test strains of facultative anaerobes: Staphylococcus aureus, Candida albicans, Enterococcus faecalis, Enterobacter agglomerans, Pseudomonas aeruginosa were analysed in the study.

2. Sensitivity to the following preparations was determined: Stomatofit A and 0.05% chlorhexidine biguanide solution.

3. Stomatofit and Stomatofit A showed antibacterial properties against a number of opportunistic microorganisms that may disturb the course of diseases of the oral mucosa

The activity of Dentosept and Dentosept A against Helicobacter pylori rods

1. Dentosept was effective against 67% of tested H. pylori bacilli.
2. Dentosept A appeared to be active against 83% of tested Helicobacter pylori strains.

Susceptibility of anaerobic bacteria isolated from a carotid atherosclerotic plaque to Dentosept

1. 23 strains of the following genera: Prevotella (4 strains), Porphyromonas (4), Tannerella (2), Fusobacterium (3), Micromonas (1), Finegoldia (3), Propionibacterium (4) and Actinomyces (2) and 4 reference strains from species: Bacteroides fragilis, Fusobacterium nucleatum, Peptostreptococcus anaerobius and Propionibacterium acnes were tested.

2. Dentosept was highly effective against all assessed anaerobic microorganisms; it showed the highest activity against Tannerella forsythia and Micromonas micros strains and appeared to be the least sensitive against the following species: Prevotella buccalis, Prevotella intermedia and Propionibacterium granulosum.

with disabilities are far more at risk of oral diseases, including dental caries and periodontal diseases due to difficulties in performing basic oral hygiene procedures. The application of the preparation in this group of patients, with unchanged hygienic habits, contributed to a significant decrease in the mean value of GI (Gingival Index) after a 10-day observation [43].

Not only doctors, but also patients claimed that products containing CHE are effective. Patients pointed out their high effectiveness in improving condition of the oral cavity in the course of inflammatory diseases of the periodontium and oral mucosa. As many as 56% rated the effect of treatment with the preparation as “very good”. No one claimed the effectiveness is unsatisfactory [44].

COMPARATIVE STUDIES WITH SYNTHETIC SUBSTANCES

Studies have also compared the efficacy of both forms: CHE and CHEB with synthetic drugs, e.g. a drug containing chlorhexidine and furacilin as active substances. The aim of this study was to assess the efficacy in comprehensive treatment of symptomatic gingivitis in generalised moderate periodontitis. The use of CHE-containing preparations in the treatment of symptomatic gingivitis in patients with generalised periodontitis appeared to be almost twice as effective as a treatment with standard therapeutic disinfectants, such as chlorhexidine or furacilin [45].

The therapeutic efficacy of a CHE-containing drug was also compared with synthetic drugs, e.g. with a preparation containing a combination of metronidazole and chlorhexidine during a 7-day periodontal treatment of generalised chronic periodontitis. The tested herbal medicines used in the treatment of extensive chronic periodontitis of a mild and moderate degree clearly revealed anti-inflammatory, antimicrobial and antiseptic effects as well as softening and deodorising ones. The preparation containing benzocaine also demonstrated an anaesthetic effect. All tested products showed a significant efficacy and are recommended for treatment of extensive chronic periodontal tissue inflammation of a mild and moderate degree, because they positively affected the dynamics of changes in clinical symptoms [46].

COMPLETE DECONTAMINATION OF THE ORAL CAVITY

The drug in the form of a mouthwash was also used to rinse periodontal pockets in patients with chronic periodontitis in
Table 2. Summary of clinical trials

<table>
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<th>Study Description</th>
<th>Clinical Trials</th>
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<tr>
<td><strong>Wysokińska-Misczczuk J, Kusa-Podkańska M, Ziętek M [35]</strong></td>
<td><strong>Evaluation of the effectiveness of Dentosept preparations</strong></td>
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<tr>
<td>Initial survey and clinical examination; verum group (Dentosept, Dentosept A) 36 people (10-69 years old); control group of 25 people (sage infusion), treated for catarrhal gingivitis and / or chronic periodontitis. First visit - assessment of periodontal pocket depth, degree of connective tissue loss (CAL) and alveolar bone loss, determination of gingival pocket bleeding index (SBI) and approximate plaque index (API). Hygienization + hygiene instruction was applied. Treatment phase - 14 days Application of preparations twice a day. Second visit - SBI and API assessment and survey of patients’ feelings. <strong>Results:</strong> verum group: API index decrease by about 49% and SBI index by 65%, control group API index decrease by about 33% and SBI index by 14%. No discoloration of the teeth was observed after the use of the tested products. Subjective assessment: no bleeding or less bleeding when brushing teeth, reduction of swelling and pain. The reduction in the values of plaque indicators and bleeding from the gingival pockets confirms the effectiveness of the treatment undertaken in the initial phase combined with the use of Dentosept and Dentosept A. The products can be used for longer than 2 weeks.</td>
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<td><strong>Zidra SI, Chirkova TD, Morozova LV, Emilienko GI, Ulyanova MA, Gorchakova NK [36]</strong></td>
<td><strong>The preparation Stomotofit (Dentosept) and its use for a combined treatment of periodontitis</strong></td>
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<td>An open-label, randomised, single-centre study with a control group; 45 patients aged 19 – 27, 38 with gingivitis and 7 with gingivitis in combination with mild local periodontitis. <strong>Results:</strong> Stomotofit (Dentosept) is characterised with marked therapeutic anti-inflammatory properties. A decrease in the Approximal Plaque Index (API) values from 96% to 30%, Papillary Marginal Attachment (PMA) from 2.5 to 0.9-1.0, Sulcus Bleeding Index (SBI) from 86% to 10%. A decrease in C-reactive protein (CRP) and antistreptolysin O levels in the gingival fluid (2-8 times).</td>
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<td><strong>Surzhansky SK, Trofmiec JK, Woskrienska OJ, Szendrik NN, Szelakowa IP [38]</strong></td>
<td><strong>Use of the herbal preparation Stomotofit in the treatment of chronic gingivitis</strong></td>
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<td>24 patients, aged 15-19 years with chronic catarrhal gingivitis. <strong>Results:</strong> Day 3: 45.8% of the subjects demonstrated a marked reduction in gingival congestion, bleeding and swelling. Day 5: 75% did not demonstrate inflammation of the marginal gingiva; in 83.3% the bleeding stopped. Day 10: in 100% no bleeding was observed; in 95.8% gingival tissue inflammation subsided completely 1 month after the treatment completion, 95.8 % showed signs of healthy gingiva and slight gingival bleeding in the area of the artificial crowns was noted in 1 patient.</td>
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<td><strong>Kuprin PV [40]</strong></td>
<td><strong>Report from an open, comparative post-research study on the efficacy and safety of the herbal medicinal preparation Stomotofit A in the comprehensive treatment of periodontitis and oral mucosa in phase IV</strong></td>
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<tr>
<td>An open, comparative randomized study, 60 patients (30 in the study group and 30 in the control group), aged 18 – 65 years. <strong>Results:</strong> A significant reduction of the PMA index value (anti-inflammatory effect), a decrease in the Oral Hygiene Index S (OHI-S) value, a decrease in the Gingivitis Severity Index (GSI), a decrease in the SBI value, analgesic effect.</td>
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<td><strong>Pietruska M, Sobaniec S, Skurska A, Dolińska E, Knaś M, Kurowski P, Pietruski J, Cechowska-Pasko M [41]</strong></td>
<td><strong>Evaluation of the effect of Dentosept mouthwash on the clinical condition of the periodontium and activity of exoglycosidases in the gingival fluid of patients with chronic periodontitis</strong></td>
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<tr>
<td>Evaluation of clinical indices of oral, gingival and periodontal hygiene; in 25 patients divided into 2 groups – the study group (15 – mechanical therapy + Dentosept) and the control group (11 – mechanical therapy) between 38 and 77 years of age suffering from moderate generalized chronic periodontitis. The clinical examination evaluated the following parameters: the Approximal Plaque Index — API; Bleeding on Probing — BOP; Periodontal Pocket Depth — PPD (in six measuring spots — in mm); Clinical Attachment Level (CAL) (in six measuring spots — in mm); Gingival Recession (GR) (in six measuring spots — in mm). <strong>Results:</strong> After the treatment: Group I – a significant reduction in API, BOP, and PPD. CAL and GR values remained at a similar level. Significant differences in the CAL values were only related to teeth with deep pockets from which the fluid was sampled. In Group II: a significant improvement of API, PPD, and CAL, while BOP and GR did not change significantly. A reduction of the Bleeding Index value was similar in both groups, although only in Group I, the difference was statistically significant. Mechanical therapy has a positive impact on the periodontal status. Improvement of the periodontal status is accompanied by a lower activity of HEX and βG in the gingival crevicular fluid. Application of Dentosept after a mechanical therapy does not improve periodontal parameters or reduce the enzymatic activity.</td>
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<td>Study</td>
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<td>Surzhansky SK, Trofimets EK [42]</td>
<td>Clinical efficacy of the combined drug Stomatofit in the comprehensive treatment of generalized periodontitis</td>
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<tr>
<td>Gerreth K, Borysewicz-Lewicka M [43]</td>
<td>Evaluation of the efficacy of the Dentosept mouthwash in the treatment of gingival inflammation in intellectually disabled patients</td>
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<tr>
<td>Chirkova TD [44]</td>
<td>Report on the fourth phase of an open post-marketing comparative randomized study on the efficacy and safety of the Stomatofit A – a phytochemical in the comprehensive treatment of inflammatory diseases of the periodontium and oral mucosa</td>
</tr>
<tr>
<td>Nemesh OM, Shylivskyy I, Honta ZM, Pupin TI [45]</td>
<td>Use of the medicine Stomatofit and Stomatofit A in the treatment of the symptomatic gingivitis with generalized parodontitis in the second degree severity</td>
</tr>
<tr>
<td>Gazhva SI, Pillipenko DI, Shkarednaya OV, Mienshikova UV [46]</td>
<td>Clinical efficacy in the treatment of conservative mild and moderate chronic extensive periapical inflammation with the application of various pharmacological preparations</td>
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<td>Konopka T, Karolewska E, Rzeszut A</td>
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<td>Sender-Janeczuk A, Kwiatkowska M</td>
<td>Effectiveness of preparations Dentosept A and Sachol in the treatment of aphthous stomatitis of the oral cavity – patient evaluation based on a questionnaire survey</td>
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<td>Kasperski J, Trzeciak H, Jaroszuk-Rogal M, Wyszyńska M</td>
<td>Influence of Dentosept and Dentosept A preparations on denture sores in patients using removable full and partial dentures</td>
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<td>Sender-Janeczuk A, Kwiatkowska M</td>
<td>Therapeutic efficacy of Dentosept A (Phytopharm Klęka S.A.) and Sachol (Jelfa S.A.) in patients with recurrent aphthous stomatitis</td>
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order to perform a complete oral decontamination during subgingival scaling. A comparative analysis of the mean values of clinical indices, conducted three months after completion of treatment with chlorhexidine and CHE-containing mouthwash, showed no statistically significant differences. However, pain subsided significantly more rapidly after the application of a CHEB-containing drug. The authors concluded that the administration of the preparation, containing CHE during the procedure of periodontal pocket rinsing in subgingival scaling, may be an effective alternative to other disinfectants, such as chlorhexidine, used for complete oral cavity decontamination, especially when the use of a plant product did not cause adverse effects in comparison to standard antiseptics used for this purpose [47].

### Table: Studies on the Use of CHEB Preparation

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<th>Study Description</th>
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<tr>
<td><strong>Kabirova MF, Usmanova IN, Khafizova AKh, Aznabayeva GM [54]</strong></td>
<td>Combination therapy with Stomatofit for young adults with recurrent aphthous stomatitis. Health, demography, ecology of Finno-Ugric peoples</td>
<td>42 patients, aged 21 – 25 years divided into 2 groups. Group I – 21 patients traditionally treated (local anesthetic, antiseptic treatment with 0.05% chlorhexidine solution and keratoplastic agent). Group II – Stomatofit administered 3 – 4 times a day for 10 – 15 days. Results: The patients with aphthous stomatitis reported a decrease in pain as early as on day 2 following the application of the preparation containing the tested extract, while complete healing was observed on day 5. In Group I, the epithelialisation process of sores was observed on day 5 onwards, while complete healing occurred on average on day 7 following the treatment.</td>
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<td><strong>Kusa-Podkańska M, Wysokińska-Miszczyk J [55]</strong></td>
<td>Dentosept and Dentosept A used for the treatment of Gingivostomatitis herpetica — case report</td>
<td>Herpetic stomatitis in a 21-year old female. Results: After one month of treatment with, among others, Dentosept (for rinsing the mouth) and Dentosept A (topically for brushing the affected areas), a complete cure and improvement of periodontal indices were observed: SBI decreased from 44% to 10% and API – from 80% to 20%.</td>
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<tr>
<td><strong>Shpak SV, Kovalchuk VV, Khodorczuk IV [56]</strong></td>
<td>Use of the Stomatofit A preparation in the comprehensive treatment of acute herpetic stomatitis in children aged 3 – 4 years</td>
<td>22 children, aged 3 – 4 years divided into 2 groups: 14 – Stomatofit A, 8 – control – standard treatment. Results: Within 5 days, the content of lysozyme in the oral fluid increased to 24.9% in the study group in comparison group and to 64.9% in the control group, which may indicate a formation of sufficiently strong antimicrobial protection. An examination of the elastase activity in the oral fluid, conducted after 5 days, revealed that in children from the comparison group, the elastase activity decreased 1.5 times in comparison with the level before the treatment, in the group of children treated comprehensively – 2.6 times. A decrease in the elastase activity and an increase in the lysozyme content in the oral fluid implies increased antimicrobial protection in the oral cavity. On the other hand, the increased urease activity indicates that treatment with the studied preparation significantly improves the oral hygiene status of children and promotes normalization of the microbiota. Stomatofit A enhances resistance to viral infections, decreases the likelihood of bacterial complications and multiplication of pathogenic microflora within the oral cavity mucosa.</td>
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<tr>
<td><strong>Janas A, Grzesiak-Janas G, Olszewski D [57]</strong></td>
<td>Results of the treatment of certain diseases with Dentosept and Dentosept A in dental surgery</td>
<td>86 patients (37 women and 49 men), aged 19 – 68 years. Dentosept and Dentosept A were applied before and after a surgical extraction of teeth in 47 patients and in difficult dentition of the lower wisdom teeth in 39 cases. Results: No postoperative complications were observed in all patients administered Dentosept and Dentosept A, before and after the surgical extraction. Swelling in the tissues of difficult dentition of the lower wisdom teeth was observed for 1 or 2 days. The majority of patients felt pain for 2 – 3 days. Only 5 patients experienced pain for up to 4 days. Besides, no allergic reactions were noted. However, in our own observations, 31 patients reported the pain relieved faster after application of both the preparations.</td>
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<td><strong>Lewandowski B, Maresch-Lewandowska M, Joanna Wojnar J, Dymek M [58]</strong></td>
<td>Dentosept A preparation in the local treatment of difficult dentition of the lower wisdom tooth</td>
<td>28 pregnant women with difficult dentition of the lower wisdom tooth. Results: A reduction of pain and inflammatory symptoms (redness, tenderness to palpation, difficulty in jaw opening, pocket exudate, gingival oedema) around the gingival pocket from day 2 to day 7 of the treatment. Clinical observations confirm that Dentosept A may be used as a topical medication for the treatment of inflammatory symptoms and alleviation of pain associated with difficult dentition of the lower wisdom teeth in patients with contraindications for antibiotic therapy and analgesics due to early pregnancy (first trimester) and its course.</td>
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TREATMENT OF INFLAMMATORY CONDITIONS OF THE ORAL MUCOSA

Many diseases of the oral mucosa are manifested with damage to the epithelium, which leads to occurrence of secondary infection of the damaged area, inflammatory symptoms and pain. Plant preparations with antimicrobial properties are successfully used to treat inflammation of the oral mucosa.

Clinical trials involving application of CHE and CHEB showed that the extracts contribute to remission of oral mucositis symptoms. In the majority of treated patients, symptoms such as congestion and/or oedema and pain subsided between 7 and 14 days after initiation of the treatment, and clinical improvement was observed already on day 2 or 3 [48]. Similar results were achieved with topical application of CHEB in the treatment of injuries of the oral mucosa. Younger patients demonstrated clinical improvement, i.e. full tissue regeneration sooner, that is already on the second day of treatment, than in older patients (after 7 days of treatment). Patients affected by chronic inflammatory diseases of the oral mucosa, such as lichen planus or necrotizing ulcerative stomatitis, recovered after 21 days [49].

In studies comparing CHEB with a product whose active substance was choline salicylate, the anaesthetic efficacy and functional properties of the herbal preparation were evaluated in patients with erosive lesions and ulcers of the oral mucosa. In both groups, the oral ulceration decreased in size and pain lessened. Besides, there were no statistically significant differences between the groups. Patients rated both preparations as effective in the treatment of erosive lesions and ulcers in the oral cavity. In their opinion, they contributed to faster healing, reduced lesion-related pain and did not cause side effects [50].

Furthermore, CHE appeared to have a positive effect in the treatment of oral mucosal lesions in patients with removable prosthetic appliances. A drug containing CHE and CHEB promoted healing of prosthetic sores, relieved pain and completely eliminated the lesions between day 3 and 14 days of treatment, depending on how extensive the lesions were [51].

APHTHOUS STOMATITIS

The efficacy of CHEB in the treatment of recurrent aphthous stomatitis was also tested in another comparative study using 0.05% chlorhexidine. It was found that in comparison to chlorhexidine, the plant-based drug immediately relieved pain, and complete epithelialisation occurred 2 days earlier (on day 5) [52].

A study comparing CHEB with a product containing choline salicylate and cetalkonium chloride as an active substance in patients with recurrent aphthous stomatitis (RAS) revealed a significant improvement in clinical condition of erosions, a gradual disappearance of the erythematous areola and mucosal ulcers, as well as faster healing of lesions after application of both preparations. There were no clear differences in the efficacy of these preparations but CHEB was characterised with a higher safety profile [53].

The aforementioned study on the efficacy of CHEB in the treatment of oral mucosal lesions also showed that chronic recurrent oral mucositis with aphthosis required a 7-day therapy [49].

Similar results, i.e. decreased pain observed as early as on day 2 of the treatment and a complete recovery on day 5, were observed for patients with aphthous stomatitis who were administered liquid containing CHE [54].

HERPETIC STOMATITIS

Results of studies confirm a highly beneficial effect of plant-based preparations containing CHE on the course of treatment of herpetic stomatitis. Virus-related gum disease can be caused by presence of herpes simplex viruses HSV1 or HSV2 (Herpes Simplex Virus, HSV), which become active when the body immunity is lowered and induce gingivitis or stomatitis (gingivostomatitis herpetica).

A beneficial effect of application of CHE and CHEB in herpetic stomatitis has been observed. After a one-month treatment, a complete recovery and improved periodontal indices were noted [55].

With regards to treatment of acute herpetic stomatitis in children aged 3-4 years, CHEB was found to be effective already after 5 days of therapy. A decrease in elastase activity and an increase in lysozyme content in oral fluid were observed, which indicates increased antimicrobial protection in the oral cavity. Besides, increased urease activity indicates that treatment with the studied preparation significantly improves the oral hygiene status of children and promotes normalisation of microbiota [56].

USE OF CHE IN DENTAL SURGERY

Preparations containing CHE or CHEB, acting as active substances, are highly effective in dental surgery after surgical procedures and in difficult dentition of lower molars. A mouthwash preparation containing CHE was applied before tooth extraction to rinse the site of the procedure. After the extraction, the CHEB version of the drug was applied on the postoperative wound in the form of a dressing. The preparation was also applied on the dental operculum in difficult dentition of lower wisdom teeth. The patients who received the preparations prior to and after tooth extraction did not demonstrate any postoperative complications. In the case of difficult dentition of lower wisdom teeth, swelling of the tissues was observed for about 1 or 2 days and pain subsided in most patients as early as after 2 or 3 days of treatment. For both the practices, CHE or CHEB-containing drugs appeared to be highly effective, which manifested by a quicker reduction of inflammation, decreased tissue oedema after a surgical procedure, faster alleviation of pain and absence of allergic reactions [57].

With regards to pregnant women, treated due to difficult dentition of the lower wisdom tooth, it has been shown that CHEB preparation, used as a topical medication for treatment and alleviation of pain and inflammatory symptoms...
associated with difficult dentition of the lower wisdom tooth, is an effective choice, particularly in women in whom antibiotics and anaesthetics are contraindicated due to early pregnancy (the first trimester) and its course [58].

APPLICATION OF CHE AND CHEB IN ADJUNCTIVE TREATMENT OF VARIOUS PATHOLOGIES OF DENTAL DISEASES

As it was mentioned before, there is a relationship between dental infections and systemic diseases. The spread of an inflammatory process mainly depends on the location of the primary infection in the oral cavity. It spreads through fasciae so bacteria penetrate into the bloodstream and reach different body regions [59].

POTENTIAL APPLICATIONS IN THE TREATMENT OF HELICOBACTER PYLORI INFECTIONS

Helicobacter pylori infections occur in 40 – 50% of adult population in developed countries and up to 90% in developing countries [60,61]. H. pylori can cause chronic gastri-tis, gastric and duodenal ulcers and some types of gastric cancer [61,62]. H. pylori infection is also a risk factor for atherosclerotic plaque formation, thereby contributing to cardiovascular diseases [61-64]. It was noted that the oral cavity is a reservoir for H. pylori and poses a potential risk for recurrence of gastric or duodenal ulcer [65].

Preparations containing CHE and CHEB have appeared to be effective against H. pylori strains isolated from peri-odontal pockets and carotid artery plaque. CHEB showed higher efficacy against H. pylori [65].

POTENTIAL APPLICATIONS FOR TREATMENT OF BACTERIAL INFECTIONS IN CARDIOVASCULAR DISEASES

Zaremba et al. suggest there is a link between bacteria inducing periodontitis and coronary atherosclerosis [66]. Since anaerobic bacteria, being one of etiological factors of periodontal disease, may be present in atherosclerotic plaque, the sensitivity of anaerobic bacteria to CHE, isolated from carotid atherosclerotic plaques, was subject to analysis.

The tested extract was highly effective against all tested anaerobic microorganisms, Gram-negative bacteria and Gram-positive bacteria, the latter being even more effective. Isolates of Gram-negative bacilli of Tannerella forysthia species appeared to be most sensitive to CHE. With regards to Gram-positive bacteria – isolates of Micromonas micros exhibited such sensitivity. It is worth stressing that preparation concentrations used in the study were between 3 and 100 times lower than those used in everyday clinical practice [67].

CONCLUSIONS

The presented study results prove high usefulness of preparations containing a composed ethanolic extract as an active substance which is obtained from: chamomile capitulum (Matricaria recutita L.), oak bark (Quercus spp.), sage leaf (Salvia officinalis L.), arnica herb (Arnica spp.), calamus rhizome (Acorus calamus L.), peppermint herb (Mentha piperita L.), thyme herb (Thymus spp.).

Preclinical studies confirmed antibacterial, antifungal and antiprotozoal properties of CHE and CHEB, as well as anti-inflammatory, immunomodulatory and astringent ones. Directions of the activity were confirmed in clinical studies which showed that drugs containing CHE and CHEB, used in prevention and comprehensive treatment of gingivitis and periodontitis as well as in diseases of the oral mucosa and pharynx of viral, bacterial, fungal and protozoan aetiology, significantly improved the effectiveness of the therapy and significantly shortened the treatment. The results of the study also prove an immuno-corrective effect of CHE, which promotes its use in prevention and comprehensive therapy of gingivitis and periodontitis. Furthermore, drugs containing the above-mentioned extract can also be successfully used for oral cavity decontamination in various diseases of teeth or the oral and pharyngeal mucosa. These preparations can be applied in dental surgery as they contribute to faster tissue regeneration and more quickly relieve pain and swelling after a surgery or difficult dentition.

Therefore, it can be concluded that CHE, both in the form of a mouthwash and with added benzocaine, i.e. CHEB, are invaluable highly effective drugs with a high safety profile. They exhibit comprehensive antimicrobial, anti-inflammatory, astringent, disinfectant and anaesthetic properties, being an invaluable alternative to synthetic drugs widely used in treatment of gingival and periodontal inflammation, and also in inflammation of the oral cavity, including aphthous and herpetic stomatitis, and in dental surgery; as in many studies, these drugs were characterised with high effectiveness, comparable to that of synthetic agents, and a higher safety profile. Obtained results indicate that application of CHE-containing preparations allowed to considerably shorten the treatment and improve indices of the quality of life.

The conducted studies have also shown that the application of the above-mentioned preparations enhances resistance to viral infections, decreases the risk of bacterial complications and accumulation of pathogenic microflora in the mucous membrane of the oral cavity. These observations justify the use of CHE preparations not only in dental practice, but also in treatment of pharyngitis and upper respiratory tract infections.

In the future, application of CHE preparations in prevention of cardiovascular diseases, including atherosclerosis, dependent on pathological bacterial flora as well as in eradication of H. pylori can be considered. However, these suggestions require further studies.

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EFFECTIVENESS OF COMPOSED HERBAL EXTRACT IN THE TREATMENT OF GINGIVITIS AND ORAL...


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Conflict of interest:
Karina Schönknecht is employed by Marketing Authorisation Holder of brands Dentosept (Stomatofit) and Dentosept A (Stomatofit A) in the Medical Affairs Department of Phytopharm Klęka SA, Poland.
No other conflict of interest is declared.

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