

REVIEW ARTICLE

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

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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.

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, antiparasitic, antifungal, antiviral and anti-inflammatory properties, which inhibits 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 Kleka 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 analgesic 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 ANTIPROTOZOAL 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 prostanoids 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, calamus 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 a 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 shown to reduce plaque markers and bleeding from gingival

pockets in combination with prior hygienisation during the 14-day efficacy evaluation. It has been shown to reduce the swelling of the gums and pain relief. Taste disturbances and tooth discoloration were not observed. Both products were positively evaluated by both doctors and patients. It was found that the preparations can be used for more than 2 weeks (however, the maximum duration of use was not given) [35].

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 – β G) 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 β G 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

<p>Kędzia A, 2000 [27]</p>	<p>The effect of Dentosept on anaerobic bacteria isolated from gingival pockets</p> <ol style="list-style-type: none"> 1.186 strains of anaerobic bacteria, isolated from 24 patients with periodontitis, were tested. Dentosept showed high activity against all tested anaerobic microbes The most sensitive (MIC≤0.6mg/ml) strains included: <i>Bacteroides</i>, <i>Porphyromonas</i>, <i>Peptostreptococcus</i>, <i>Propionibacterium</i> <i>Prevotella</i> and <i>Fusobacterium</i> were less sensitive <i>Peptococcus</i>, <i>Clostridium</i> and <i>Veillonella</i> were much less susceptible (MIC 5 – ≥20 mg/ml)
<p>Kędzia A, 2006 [28]</p>	<p>The activity of Dentosept A against anaerobic bacteria isolated from oral cavity infections</p> <ol style="list-style-type: none"> 1. 118 strains of anaerobic bacteria isolated from 21 patients with infections of oral cavity were tested Dentosept A showed high activity against all tested anaerobic microbes <i>Prevotella</i> and <i>Porphyromonas</i> were most sensitive (MIC in ranges =0.6 – 1.2 mg/ml) <i>Fusobacterium</i> and <i>Bacteroides</i> were less sensitive (MIC=0.6 – 1.2 mg/ml) <i>Eubacterium</i> (MIC=0.6 mg/ml) and <i>Micromonas</i> (MIC =0.6 – 2.5 mg/ml) were most of Gram-positive anaerobic bacteria <i>Veillonella</i> spp. (MIC ranges 5.0- =20.0 mg/ml) were much less susceptible
<p>Sender-Janeczek A, Kędzia A, Kwiatowska M, Ziętek M [29]</p>	<p>Antimicrobial efficacy of Dentosept and 0.1% chlorhexidinegluconate on anaerobic bacteria</p> <ol style="list-style-type: none"> 1. Anaerobic bacteria were isolated from 24 patients with advanced chronic periodontitis or gingivitis or mucosal ulceration 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. 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
<p>Moroz J, Kurnatowski P [30]</p>	<p>In vitro effect of selected mouthwashes on standard fungal strains</p> <ol style="list-style-type: none"> 1. 8 reference fungal strains were investigated: <i>C. albicans</i> x3, <i>C. dubliniensis</i>, <i>C. glabrata</i>, <i>C. krusei</i>, <i>C. parapsilosis</i> and <i>C. tropicalis</i> 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% The largest inhibition zones were produced by Dentosept, Chlorhexidine and Colgate The smallest inhibition zones were produced by Octenidol 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 The lowest MIC values, indicating the strongest potential activity, were obtained for Dentosept A, followed by chlorhexidine The highest MIC values, indicating the lowest activity, was calculated for Curasept and Octenidol
<p>Radwan-Oczko M, Kędzia A, Michalak A [31]</p>	<p>The activity of Dentosept A against yeast-like fungi</p> <ol style="list-style-type: none"> 1. The studies focused on 30 strains of yeast-like fungi, including <i>Candida</i> (26 strains), <i>Geotrichum</i> (2), <i>Rhodotorula</i> (1) and <i>Saccharomyces</i> (1), which were isolated from infections, apart from 6 strains from model species: <i>Candida albicans</i> – x2, <i>Candida glabrata</i>, <i>Candida krusei</i>, <i>Candida parapsilosis</i>, <i>Candida tropicalis</i> After 15 minutes of exposure to the preparation, 81% of fungal strains were eliminated, and after 30 minutes, all tested strains from <i>Candida</i> type were eliminated and a fungicidal activity (MFC) towards <i>Geotrichum candidum</i>, <i>Rhodotorula mucilaginosa</i> and <i>Saccharomyces cerevisiae</i> strains was observed as early as after 15 minutes
<p>Kędzia A, Kochańska B, Póljanowska M, Kędzia AW, Wojtaszek-Słomińska A, Wierzbowska M, Kwapisz E [32]</p>	<p>The effect of Dentospet on yeast-like fungi responsible for infections of the oral cavity</p> <ol style="list-style-type: none"> 1.128 strains of fungi: <i>Candida</i> (105 strains), <i>Geotrichum</i> (16), <i>Rhodotorula</i> (5), <i>Saccharomyces</i> (2) isolated from oral cavity infections Dentosept was the most active towards <i>Candida mesenterica</i> and <i>C.parapsilosis</i> (MIC≤5.0 mg/ml) and the least active towards <i>C. dubliniensis</i>, <i>C. guilliermondii</i> and <i>C. krusei</i> (MIC 15.0 – ≥ 20.0 mg/ml)

<p>Moroz J, Kurnatowska AJ, Kurnatowski P [33]</p>	<p>The <i>in vitro</i> activity of selected mouthwashes on the reference strains of <i>Trichomonas tenax</i> and <i>Entamoeba gingivalis</i></p> <p>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, Dentosept A, Eludril Classic, Listerine Total Care, Octenidol, Oral-B Pro-Expert Clinic Line, Sylveco and Tinctura salviae</p> <p>2. All undiluted mouthwashes, tested in this work, exhibited a lethal impact on both <i>Entamoeba gingivalis</i> and <i>Trichomonas tenax</i> after 1, 10 and 30 minutes, respectively</p> <p>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</p>
<p>Anisimova IV, Nagajeva MO [49]</p>	<p>Clinical and laboratory justification for topical application of the herbal preparations Stomatofit and Stomatofit A in complex diseases of the oral mucosa</p> <p>1. Test strains of facultative anaerobes: <i>Staphylococcus aureus</i>, <i>Candida albicans</i>, <i>Enterococcus faecalis</i>, <i>Enterobacter agglomerans</i>, <i>Pseudomonas aeruginosa</i> were analysed in the study</p> <p>2. Sensitivity to the following preparations was determined: Stomatofit A and 0.05% chlorhexidine biguanide solution</p> <p>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</p>
<p>Kędzia A, Wierzbowska M, Kufel A [65]</p>	<p>The activity of Dentosept and Dentosept A against <i>Helicobacter pylori</i> rods</p> <p>1. Dentosept was effective against 67% of tested <i>H. pylori</i> bacilli</p> <p>2. Dentosept A appeared to be active against 83% of tested <i>Helicobacter pylori</i> strains</p>
<p>Kędzia A, Wierzbowska M, Kufel A, Ciecierski M [67]</p>	<p>Susceptibility of anaerobic bacteria isolated from a carotid atherosclerotic plaque to Dentosept</p> <p>1. 23 strains of the following genera: <i>Prevotella</i> (4 strains), <i>Porphyromonas</i> (4), <i>Tannerella</i> (2), <i>Fusobacterium</i> (3), <i>Micromonas</i> (1), <i>Fingoldia</i> (3), <i>Propionibacterium</i> (4) and <i>Actinomyces</i> (2) and 4 reference strains from species: <i>Bacteroides fragilis</i>, <i>Fusobacterium nucleatum</i>, <i>Peptostreptococcus anaerobius</i> and <i>Propionibacterium acnes</i> were tested</p> <p>2. Dentosept was highly effective against all assessed anaerobic microorganisms; it showed the highest activity against <i>Tannerella forsythia</i> and <i>Micromonas micros</i> strains and appeared to be the least sensitive against the following species: <i>Prevotella buccalis</i>, <i>Prevotella intermedia</i> and <i>Propionibacterium granulosum</i></p>

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

Treatment of gingivitis and periodontitis	
<p>Wysokińska-Miszczuk J, Kusa-Podkańska M, Ziętek M [35]</p>	<p>Evaluation of the effectiveness of Dentosept preparations</p> <p>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.</p> <p>Results: 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%.</p> <p>No discoloration of the teeth was observed after the use of the tested products.</p> <p>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.</p>
<p>Zidra SI, Chirkova TD, Morozova LV, Emilenko GI, Ulyanova MA, Gorchakova NK [36]</p>	<p>The preparation Stomatofit (Dentosept) and its use for a combined treatment of periodontitis</p> <p>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.</p> <p>Results: Stomatofit (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%.</p> <p>A decrease in C-reactive protein (CRP) and antistreptolysin O levels in the gingival fluid (2-8 times).</p>
<p>Surzhansky SK, Trofimiec JK, Woskriesienska OJ, Szendrik NN, Szelakowa IP [38]</p>	<p>Use of the herbal preparation Stomatofit in the treatment of chronic gingivitis</p> <p>24 patients, aged 15-19 years with chronic catarrhal gingivitis.</p> <p>Results: Day 3: 45.8% of the subjects demonstrated a marked reduction in gingival congestion, bleeding and swelling.</p> <p>Day 5: 75% did not demonstrate inflammation of the marginal gingiva; in 83.3% the bleeding stopped.</p> <p>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.</p>
<p>Kuprin PV [40]</p>	<p>Report from an open, comparative, randomized post-research study on the efficacy and safety of the herbal medicinal preparation Stomatofit A in the comprehensive treatment of periodontitis and oral mucosa in phase IV</p> <p>An open, comparative randomized study, 60 patients (30 in the study group and 30 in the control group), aged 18 – 65 years.</p> <p>Results: 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.</p>
<p>Pietruska M, Sobaniec S, Skurska A, Dolińska E, Knaś M, Kurowski P, Pietruski J, Cechowska-Pasko M [41]</p>	<p>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</p> <p>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.</p> <p>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).</p> <p>Results: 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.</p> <p>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.</p>

<p>Surzhansky SK, Trofimets EK [42]</p>	<p>Clinical efficacy of the combined drug Stomatofit in the comprehensive treatment of generalized periodontitis</p> <p>49 volunteers with chronic generalized periodontitis took part in the study. Assessment of the periodontal status with the following hygienic and periodontic indices: Green-Vermillion, PMA, Müllemann gingival bleeding, periodontal pocket depth, the Russel Parodontic Index. Treatment of local inflammation of periodontal tissues by: removal of factors increasing retention of plaque, disinfection of the oral cavity, professional hygiene with removal of soft deposits on teeth, tartar deposits above and below the gums, haemostasis with 3% solution of hydrogen peroxide, irrigation of periodontal pockets with 0.1% solution of chlorhexidine digluconate. Next, application of a complex plant extract in the study group for 7 days. Results: Hygienization significantly improved the condition of the oral cavity in patients in both groups. One month after the treatment completion, oral hygiene indices levels were high in the study group; in the control group, the condition of the oral cavity was satisfactory (there was a tendency for deterioration).</p>
<p>Gerreth K, Borysewicz-Lewicka M [43]</p>	<p>Evaluation of the efficacy of the Dentosept mouthwash in the treatment of gingival inflammation in intellectually disabled patients</p> <p>31 students of a special needs school, aged 7 – 16 (of whom 29 mildly and 2 moderately intellectually disabled) Results: A change in the gingival condition (inflammation) according to the Gingival Index (GI): after a 10-day application of the mouthwash, the condition of the gums improved – the Dentosept preparation appeared to be an effective herbal mouthwash, which can be used as a therapeutic agent for gingival inflammation in disabled patients.</p>
<p>Chirkova TD [44]</p>	<p>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</p> <p>60 patients, divided according to the randomization schedule into two groups, each consisting of 30 subjects (one group treated with Stomatofit A, the other with Stomatofit). Efficacy parameters included: the Oral Hygiene Index (OHS-I), inflammation dynamics index PMA, Papillary Bleeding Index (PBI), pain score on the visual-analogue scale, integral effectiveness assessment, subjective effectiveness assessment, clinical assessment, safety assessment. Results: Degree of oral hygiene, a significant reduction in inflammatory parameters and reduction in pain sensation were observed in both groups. No adverse effects were noted. 56% of the subjects assessed the effect of treatment with the preparations as „very good” or „good” – 44% Stomatofit A and 23% Stomatofit). No one rated the effectiveness as unsatisfactory.</p>
<p>Nemesh OM, Shylyvskyy I, Honta ZM, Pupin TI [45]</p>	<p>Use of the medicine Stomatofit and Stomatofit A in the treatment of the symptomatic gingivitis with generalized parodontitis in the second degree severity</p> <p>A comprehensive treatment of 98 patients with the second degree severity of generalized periodontitis, aged 35 – 60 years, included into 3 groups: Main I Stomatofit mouthwash, the Control group – bigluconate chlorhexidine 0.05 – 0.2 % solution, and 1:500 diluted furaciline, Main II Stomatofit A applied to the mucous membrane of the gums. Results: A significant reduction of pain and an increased feeling of freshness in the oral cavity in groups applying preparations with the tested extract as early as on day 3 o 4 following the implementation of treatment. A significant decrease in the Papillary – Marginal Attachment Index (PMA) value in both study groups, as compared to the control group (2.5-fold and 2.8-fold, for the versions without and with benzocaine, respectively) and a 2-fold decrease in the Approximal Plaque Index (API) value.</p>
<p>Gazhva SI, Pillipenko DI, Shkarednaya OV, Mienshikova UV [46]</p>	<p>Clinical efficacy in the treatment of conservative mild and moderate chronic extensive periapical inflammation with the application of various pharmacological preparations</p> <p>179 patients, aged 20 – 55 years, with the following diagnoses: Mild CGP – 48.6% Moderate CGP – 51.4% of the patients, were divided into 3 groups: I – Asepta, adhesive balm, composed of metronidazole and chlorhexidine, II – Stomatofit, III - Stomatofit A. Periodontal tissues condition has been determined using IG indices. PMA and PI as well as orthopantomograms have been studied. All medicines are recommended for the treatment of mild and moderate CGP. Results: The improvement in the clinical symptoms/signs, as shown by the index assessment, proves high efficacy of these medicines. Positive dynamics of the periodontal condition in terms of all hygienic and periodontal indices were examined.</p>

<p>Konopka T, Karolewska E, Rzeszut A [47]</p>	<p>Clinical evaluation of Dentosept in complete mouth disinfection</p> <p>20 subjects, aged 38 – 55 years with chronic periodontitis. The subjects were clinically monitored at baseline and 3 months following the treatment. The following indices were used: the modified O'Leary Plaque Index, (PI) Approximal Plaque Index (API) according to Lange et al., Papilla Bleeding Index (PBI) according to Saxer and Muhleman. The pocket depth was also recorded.</p> <p>Results: A statistically significant improvement of each clinical parameter was noted on both sides of the mouth, either treated with Dentosept or with chlorhexidin.</p>
<p>Treatment of the oral mucositis</p>	
<p>Ron GI, Chernysheva ND [48]</p>	<p>Use of Stomatofit in the treatment of oral mucosa diseases</p> <p>25 patients with oral mucositis, 3 – 4 times a day for 10 – 15 days.</p> <p>Results: Remission of oral mucositis symptoms, i.e. reduction or disappearance of congestion and/or oedema and pain as early as on day 2 or 3 of the treatment. The symptoms subsided within 7 – 14 days in most subjects.</p>
<p>Anisimova IV, Nagajeva MO [49]</p>	<p>Clinical and laboratory justification for topical application of the herbal preparations Stomatofit and Stomatofit A in the comprehensive treatment of diseases of the oral mucosa</p> <p>20 patients, aged 35 – 75 years with diseases of the oral mucosa.</p> <p>Results: Full tissue regeneration after only two days, and in older patients – after 7 days of the treatment. In the case of chronic recurrent oral mucositis, aphthae disappeared within 7 days, whereas chronic inflammatory diseases of the oral mucosa, such as lichen planus and necrotizing ulcerative stomatitis, subsided after 21 days.</p>
<p>Sender-Janeczek A, Kwiatkowska M [50]</p>	<p>Effectiveness of preparations Dentosept A and Sachol in the treatment of aphthous stomatitis of the oral cavity – patient evaluation based on a questionnaire survey</p> <p>Randomized studies, 70 patients, aged 21 – 80 years, divided into 2 groups: Group I (35), with topical administration of Dentosept A and Group II (35), with administration of Sachol.</p> <p>Results: A clinical trial revealed that the results regarding the decrease in the size of the ulcer in the oral cavity were comparable in both study groups (no statistically significant differences). There were no significant differences between the study groups in terms of pain reduction on the VAS scale. No statistically significant differences were noted in the examined groups regarding the flavour, ease of application and adherence of the product to the oral mucosa.</p>
<p>Kasperski J, Trzeciak H, Jaroszuk-Rogal M, Wyszyńska M [51]</p>	<p>Influence of Dentosept and Dentosept A preparations on denture sores in patients using removable full and partial dentures</p> <p>82 subjects, aged 51 – 74 years.</p> <p>Results: A reduction in size of the treated oral ulceration and reduction of pain; the differences were statistically insignificant. In the patients' opinion, both preparations are effective in the treatment of erosive lesions and ulcers in the oral cavity, contribute to faster healing, reduce pain accompanying the lesions and have no side effects. A positive effect of the tested extract in the treatment of lesions of the oral mucosa in patients with removable dentures. The tested extract facilitated the treatment of prosthetic sores, reduced pain and contributed to complete subsidence of lesions within 3 – 14 days of the treatment, depending on the extent of the lesions.</p>
<p>Zakirova ID, Kiekbaeva ER [52]</p>	<p>Changes in the quality of life of patients with recurrent aphthous stomatitis treated with the Stomatofit A product</p> <p>64 patients aged, 25 – 35 years, divided into 2 groups: Group I – 0.05% chlorhexidine + keratoplastic compound agent "Aevit" (32 patients), Group II – Stomatofit A (32 patients), and administered the preparation 3 – 4 times a day, not longer than 5 days.</p> <p>Results: In Group I, aphthae started to subside on day 5 of the treatment. Complete epithelialization occurred on day 7. In Group 2, the patients immediately noted a reduction of pain. Complete epithelialization occurred on day 5. The application of Stomatofit A drug in the comprehensive treatment of recurrent aphthous stomatitis allowed to shorten the treatment and improve the quality of life indices.</p>
<p>Sender-Janeczek A, Kwiatkowska M [53]</p>	<p>Therapeutic efficacy of Dentosept A (Phytopharm Kłęka S.A.) and Sachol (Jelfa S.A.) in patients with recurrent aphthous stomatitis</p> <p>Evaluation of the therapeutic efficacy of Dentosept A and Sachol (Cholini salicylas + Cetalkonii chloridum) in patients with aphthous stomatitis. 70 patients with recurrent aphthous stomatitis, aged 21 – 80 years. In Group I, the patients were applied Dentosept A and Group II was applied Sachol. A clinical examination of lesions on the oral mucosa was conducted prior to the initiation of the therapy. Then, control examination were made on days 4 and 7 following the implementation of the product.</p> <p>Results: The application of both Dentosept A and Sachol resulted in a significant improvement of the clinical condition of the lesions in the oral mucosa. The differences between the groups were statistically insignificant.</p>

<p>Kabirova MF, Usmanova IN, Khafizova AKh, Aznabayeva GM [54]</p>	<p>Combination therapy with Stomatofit for young adults with recurrent aphthous stomatitis. Health, demography, ecology of Finno-Ugric peoples</p> <p>42 patients, aged 21 – 25 years divided into 2 groups. Group I – 21 patients traditionally treated (local anesthetic, antiseptic treatment with 0.05% chlohexidine solution and keratoplastic agent). Group II – Stomatofit administered 3 – 4 times a day for 10 – 15 days.</p> <p>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.</p>
<p>Kusa-Podkańska M, Wysockińska- Miszczuk J [55]</p>	<p>Dentosept and Dentosept A used for the treatment of <i>Gingivostomatitis herpetic</i> — case report</p> <p>Herpetic stomatitis in a 21-year old female.</p> <p>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%.</p>
<p>Shpak SV, Kovalchuk VV, Khodorczuk IV [56]</p>	<p>Use of the Stomatofit A preparation in the comprehensive treatment of acute herpetic stomatitis in children aged 3 – 4 years</p> <p>22 children, aged 3 – 4 years divided into 2 groups: 14 – Stomatofit A, 8 – control – standard treatment.</p> <p>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.</p> <p>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.</p>
<p>Janas A, Grzesiak-Janak G, Olszewski D [57]</p>	<p>Results of the treatment of certain diseases with Dentosept and Dentosept A in dental surgery</p> <p>86 patients (37 women and 49 men), aged 19 – 68 years.</p> <p>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.</p> <p>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.</p> <p>Besides, no allergic reactions were noted. However, in our own observations, 31 patients reported the pain relieved faster after application of both the preparations.</p>
<p>Lewandowski B, Maresch- Lewandowska M, Joanna Wojnar J, Dymek M [58]</p>	<p>Dentosept A preparation in the local treatment of difficult dentition of the lower wisdom tooth</p> <p>28 pregnant women with difficult dentition of the lower wisdom tooth.</p> <p>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.</p> <p>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.</p>

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 con-

cluded 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].

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 prosthodontic 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 ulcerations, 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 gastritis, 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 periodontal 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 immunocorrective 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.

REFERENCES

1. Kozłowska M, Streit D, Kozłowski P, Cuch B. [Analysis of oral hygiene-related habits and behaviours]. *J Edu Health Sport*. 2015;5(9):95-101 (in Polish).
2. Niedzielska I, Wziątek-Kuczmik D. [The effects of dentogenic infection foci on internal organ disease – literature Review]. *Chir Pol*. 2007;9(2):92-96 (in Polish).

3. Konopka T, Mendak M. [Prevalence of Oral Mucosal Diseases in Patients of Specialistic Clinic in Wrocław in the Years 1992–2003]. *Dent Med Probl.* 2004;41(4):717-725 (in Polish)
4. Górska R, Nowak M. [Selected issues about diagnosis and treatment of the oral mucose membrane. *Pol Przegl Otolaryngol.* 2017;2(6):14-22; doi: 10.5604/01.3001.0010.1026 (in Polish).
5. Kwiatkowska A, Mielczarek A, Gajewski T. [The use of essential oils in oral hygiene products]. *Nowa Stomatol* 2017;3:148-155 (in Polish).
6. Kozłowski Z, Konopka T. [Selected Problems from Pharmacotherapy of Oral Mucosa Diseases]. *Dent Med Probl.* 2004;41:119-123 (in Polish).
7. Soković M, Glamočlija J, Marin PD, Brkić D, van Griensven LJ. Antibacterial effects of the essential oils of commonly consumed medical herbs using an in vitro model. *Molecules* 2010;15:7532-7546.
8. Grys A, Kania M, Baraniak J. [Chamomile – common herb plant with multiple phytochemical properties]. *Post Fitoter.* 2014;2:90-93 (in Polish)
9. Kędzia B. [Antimicrobial Activity of Chamomile and Its Components]. *Herba Pol* 1991;37:29-38 (in Polish)
10. Kędzia A. [Effect of alcoholic extract of chamomile flowers (AZULAN) on anaerobic bacteria]. *Herba Polonica.* 1999;4(45):362-367 (in Polish)
11. Koper J, Szczerba J, Pulawska M, Zajdel D. The use of medicinal plants in dental treatment, *Herba Polonica* 2010;1(56):97-107
12. Ghorbani A, Esmailizadeh M. Pharmacological properties of *Salvia officinalis* and its components *J Tradit Complement Med.* 2017;7:433–440.
13. Badiie P, Nasirzadeh AR, Motaffaf M. Comparison of *Salvia officinalis* L. essential oil and antifungal agents against candida species. *J Pharm Technol Drug Res.* 2012;1:7
14. Tada M, Okuno K, Chiba K, Ohnishi E, Yoshii T. Antiviral diterpens from *Salvia officinalis*. *Phytochemistry.* 1994;35:539-541.
15. Baricevic D, Sosa S, Della-Loggia R, Tubaro A, Simonowska B, Krasna A, Zupanacic A. Topical anti-inflammatory activity of *Salvia officinalis* L. leaves: the relevance of ursolic acid. *J Ethnoph.* 2001;75:123-132.
16. Kriplani P, Guarve K, Baghael US. *Arnica montana* L. – a plant of healing: review. *J Pharm Pharmacol.* 2017;69:925-945.
17. Iauk L, Lo Bue AM, Milazzo I, Rapisarda A, Blandino G. Antibacterial activity of medicinal plant extracts against periodontopathic bacteria. *Phytother Res.* 2003;17:599-604.
18. Kalembe D, Kunicka A. Antibacterial and antifungal properties of essential oils. *Curr Med Chem.* 2003;10:813-829.
19. Imelouane B, Amhamdi H, Wathelet JP, Wathelet M, Ankit M, Khedid K, El Bachiri A. Chemical composition and antimicrobial activity of essential activity of essential oil of *Thymus vulgaris* from Eastern Morocco. *Int J Agricult Biol.* 2009;2:205-208.
20. Soković MD, Vukojevic J, Marin PD, Brkić DD, Vajs V, van Griensven LJLD. Chemical composition of essential oils of *Thymus* and *Mentha* species and their antifungal activities. *Molecules.* 2009;14:238-249.
21. McKay D, Blumberg JB. A review of the bioactivity and potential healthy benefits of peppermint tea (*Mentha piperita* L.). *Phytother Res.* 2006;20:619-633
22. Li Y, Liu Y, Ma A, Bao Y, Wang M, Sun ZL. In vitro antiviral, anti-inflammatory, and antioxidant activities of the ethanol extract of *Mentha piperita* L. *Food Sci Biotechnol.* 2017;26:1675.
23. Phongpaichit S, Pujenjob N, Rukachaisirikul V, Ongsakul, M. Antimicrobial activities of the crude methanol extract of *Acorus calamus* Linn. *Songklanakarin J Sci Technol.* 2005;27(Suppl. 2):517-523.
24. Deryabin DG, Tolmacheva AA. Antibacterial and Anti-Quorum Sensing Molecular Composition Derived from *Quercus cortex* (Oak bark). *Extract Molecules* 2015;20:17093-108.
25. Dentosept. Summary of Product Characteristics, [<https://pub.rejestrymedyczne.csioz.gov.pl/Pobieranie.aspx?type=1768>. Access 05.03.2021] (in Polish).
26. Dentosept A. Summary of Product Characteristics, [<https://pub.rejestrymedyczne.csioz.gov.pl/ProduktSzczegoly.aspx?id=1769>. Access 05.03.2021] (in Polish).
27. Kędzia A. [The effect of Dentosept on anaerobic bacteria isolated from gingival pockets] *Czas Stomatol.* 2000;53(8):479-484 (in Polish).
28. Kędzia A. [The activity of Dentosept A against anaerobic bacteria isolated from infections of oral cavity]. *Post Fitoter.* 2006;1:11-15 (in Polish).
29. Sender-Janeczek A, Kędzia A, Kwiatowska M, Ziętek M. Antimicrobial efficacy of Dentosept® and 0,1% chlorhexidine gluconate on anaerobic bacteria. *J Stomatol.* 2013(66):774-786.
30. Moroz J, Kurnatowski P. The in vitro activity of selected mouthrinses on standard strains of fungi. *Ann Parasitol.* 2017;63:331-339.
31. Radwan-Oczko M, Kędzia A, Michalak A. [The activity of Dentosept A against yeast-like fungi]. *Protet Stomatol.* 2013;63:262-271 (in Polish).
32. Kędzia A, Kochańska B, Półjanowska M, Kędzia AW, Wojtaszek-Słomińska A, Wierzbowska M, Kwapisz E. Activity of Dentosept on yeastlike fungi responsible for infections of oral cavity. *Pol J Envir Stud.* 2008;17:9-13.
33. Moroz J, Kurnatowska AJ, Kurnatowski P. The in vitro activity of selected mouthrinses on the reference strains of *Trichomonas tenax* and *Entamoeba gingivalis*. *Annals of Parasitology* 2019;65(3):257-265; doi: 10.17420/ap6503.208
34. Rathee P, Chaudhary H, Rathee S, Rathee D, Kumar V, Kohli K. Mechanism of action of flavonoids as anti-inflammatory agents: a review. *Inflamm Allergy Drug Targets.* 2009;8:229-35.
35. Wysokińska-Miszczuk J, Kusa-Podkańska M, Ziętek M, [Evaluation of the effectiveness of Dentosept preparations], In house study report, Lublin 2008 (in Polish)
36. Zidra SI, Chirkova TD, Morozova LV, Emilenko GI, Ulyanova MA, Gorchakova NK. The preparation “Stomatofit (Dentosept)” and its Use for the Combined Treatment of Parodontitis. 2002, “Krasnogorsklesredstva” Moscow State Medical Stomatological University, Moscow, Russia [<http://www.dentosept.info/download/dentospet-research-Zidra2002.pdf> Access 05.03.2021].
37. Szalewski L, Szalewska M, Wójcik D, Bożyk A, Berger M. [Natural herbs used in dentistry]. *e- Dentico* 2015;2(54):102-108 (in Polish).
38. Surzhansky SK, Trofimiec JK, Woskriesienska OJ, Szendrik NN, Szelakowa IP. [The use of the herbal preparation “Stomatofit” in the treatment of chronic gingivitis]. *Collection of Articles,* 2011;2:203-207 (in Russian).
39. Ezzo PJ, Cutler CW. Microorganisms as risk indicators for periodontal disease. *Periodontol* 2000. 2003;32:24-35. doi: 10.1046/j.0906-6713.2003.03203.x. PMID: 12756031.
40. Kuprin PV. [Report from an open, comparative, randomized post-research study on the efficacy and safety of the herbal medicinal preparation “Stomatofit A” in the comprehensive treatment of periodontitis and oral mucosa in phase IV] *Mod Dentist.* 2010;4,45-50 (in Russian).
41. Pietruska M, Sobaniec S, Skurska A, Dolińska E, Knaś M, Kurowski P, Pietruski J, Cechowska-Pasko M. [Evaluation of Dentosept® mouthrinse effect on periodontal status and on the activity of exoglycosidases in crevicular fluid in patients with chronic periodontitis]. *Czas Stomatol* 2009;62(4):254-261 (in Polish).
42. Surzhansky SK, Trofimets EK. [Clinical efficacy of the combined drug “Stomatofit” in the comprehensive treatment of generalized periodontitis]. *Mod Dentist.* 2011;1:53-55 (in Russian).

43. Gerreth K, Borysewicz-Lewicka M. [Efficiency of Dentosept mouthrinse in the treatment of gingivitis in intellectually disabled patients]. *Dental Forum* 2009;1:45-49 (in Polish).
44. Chirkova TD. [Report on the fourth phase of an open post-marketing comparative randomized study of the efficacy and safety of the Stomatofit A phytochemical in the complex treatment of inflammatory diseases of the periodontium and oral mucosa. Moscow State Medical and Dental University. Moscow, 2009 (in Russian).
45. Nemesh OM, Shylivskyy I, Honta ZM, Pupin TI. [The use of the medicine Stomatofit and Stomatofit A in the treatment of the symptomatic gingivitis with generalized parodontitis in the second phase of the ponderosity. *Mod Dentist*. 2011;3:69-71] (in Russian).
46. Gazhva SI, Pillipenko DI, Shkarednaya OV, Mienshikova UV. [Clinical efficacy in the treatment of conservative mild and moderate chronic widespread periapical inflammation with the use of various pharmacological preparations. *Clinic Dentist*. 2011;3:34-36 (in Russian).
47. Konopka T, Karolewska E, Rzeszut A. [Clinical evaluation of Dentosept in full mouth disinfection]. *Czas Stomat* 2010;63(1):34-40 (in Polish).
48. Ron GI, Chernysheva ND. [The use of Stomatofit in the treatment of diseases of the oral mucosa. *Ural State Medical Academy, Yekaterinburg, Ther Dentist*. 2010;1:5 (in Russian).
49. Anisimova IV, Nagajeva MO. [Clinical and laboratory justification for the local application of the herbal preparations "Stomatofit" and "Stomatofit A" in the comprehensive treatment of diseases of the oral mucosa]. *Today's Dentistry* 2010;95:23 (in Russian).
50. Sender-Janeczek A, Kwiatkowska M. [Effectiveness of preparations Dentosept A[®] and Sachol[®] in treatment of aphthous stomatitis of the oral cavity – patient evaluation based on a questionnaire survey]. *Mag Stomatol*. 2016;6:78-82 (in Polish).
51. Kasperski J, Trzeciak H, Jaroszuk-Rogal M, Wyszyńska M. [Influence of Dentosept and Dentosept A preparations on denture sores in patients using removable full and partial dentures]. *Mag Stomatol*. 2011;6:121-124 (in Polish).
52. Zakirova ID, Kiekbaeva ER. Changes in the quality of life of patients with retaining aphthosis statomit use in the treatment of the product "Stomatofit A". *Eu Sc J* 2020;1(53):44-45 (in Russian).
53. Sender-Janeczek A, Kwiatkowska M. [Therapeutic efficacy of the Dentosept A[®] Phytopharm Kłęka S.A.) and Sachol[®] (Jelfa S.A.) in patients with recurrent aphthous stomatitis]. *Nowa Stomatol* 2015;20:105-109 (in Polish).
54. Kabirova MF, Usmanova IN, Khafizova AKh, Aznabayeva GM. [Combination therapy with Stomatofit for young adults with recurrent aphthous stomatitis. Health, demography, ecology of finno-ugric peoples. *Health, Demography, Ecology of The Finno-Ugric Peoples*. 2015;3:41-42 (in Russian).
55. Kusa-Podkańska M, Wysokińska-Miszczuk J. [Dentosept and Dentosept A used for the treatment of Gingivostomatitis herpetica – case report]. *Stomatol Wspolcz* 2010;17:16-19 (in Polish).
56. Shpak SV, Kovalchuk VV, Khodorczuk IV. [The use of the preparation "Stomatofit A" in the complex treatment of acute herpetic stomatitis in children aged 3-4 years. *Clin Tests* 2012;19:10-11] (in Russian).
57. Janas A, Grzesiak-Janias G, Olszewski D. [Results of treatment of some diseases in dental surgery with Dentosept and Dentosept A]. *Porad Stomatol* 2008;10:249-252 (in Polish).
58. Lewandowski B, Maresch-Lewandowska M, Joanna Wojnar J, Dymek M. [Dentosept A preparation in the local treatment of difficult eruption of lower wisdom tooth]. *Mag Stomatol*. 2010;10:58-61 (in Polish).
59. Piekoszewska-Ziętek P, Turska-Szybka A, Olczak-Kowalczyk D. [Odontogenic infections – review of the literature], *Nowa Stomatol*. 2016;2:120-134; doi: 10.5604/14266911.1208252.
60. Knigge KL. [The role of *Helicobacter pylori* in diseases of the digestive system]. *Med Po Dypl* 2002;11:79 (in Polish).
61. Łęowska-Kochaniak A. [Mechanism of the pathogenic activity of *Helicobacter pylori*]. *Post Microbiol* 1994;33:447 (in Polish).
62. Wroblewski LE, Peek RM Jr., Wilson KT. *Helicobacter pylori* and Gastric Cancer: Factors That Modulate Disease Risk. *Clin Microbiol Rev*. 2010;23:713-739
63. De Luis D, Lahera M, Canton R, Boixeda D, San Román AL, Aller R, de La Calle H. Association of *Helicobacter pylori* infection with cardiovascular and cerebrovascular disease in diabetes patients. 1998;21:1129
64. Pieniżek P, Karczewska E, Duda A, Tracz W, Pasowicz M, Konturek SJ. Association of *Helicobacter pylori* infection with coronary heart disease. *J Physiol Pharmacol* 1999;50:743-751
65. Kędzia A, Wierzbowska M, Kufel A. [The activity of Dentosept and Dentosept A against *Helicobacter pylori* rods]. *Post Fitoter* 2007;1:1-7 (in Polish).
66. Zaremba M, Górska R, Suwalski P. [Assessment of the incidence of bacteria associated with periodontal disease in atherosclerotic coronary artery plaque]. *Czas Stomatol* 2005;58:293-311 (in Polish)
67. Kędzia A, Wierzbowska M, Kufel A, Ciecierski M. [Activity of Dentosept, Dentosept A and Salviasept against microaerophilic bacteria isolated from the carotid atherosclerotic plaque]. *Post Fitoter* 2012;1:11-14 (in Polish).

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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 Kłęka SA, Poland.

No other conflict of interest is declared.

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