Title: PHARMACEUTICAL COMPOSITIONS CONTAINING HERBAL BASED ACTIVE INGREDIENTS FOR APPLICATION IN HUMAN AND VETERINARY MEDICINE

Abstract: The present invention refers to pharmaceutical composition on the basis of extracts/pulverized plant materials/essential oils of: lichen Old Man's Beard (Usnea barbata L.) and/or Greek oregano (Origanum heracleoticum L.) and/or Mountain tea (Satureja montana L.) and/or Winter savory (Satureja montana L.), as well as preparations in a form of compressed lozenges, solution, gel and spray for the application in the treatment of inflammation of mucous membranes of the mouth and throat and for the preventive and therapeutic purposes in human and veterinary medicine.
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PHARMACEUTICAL COMPOSITIONS CONTAINING HERBAL BASED ACTIVE
INGREDIENTS FOR APPLICATION IN HUMAN AND VETERINARY MEDICINE

Technical field

The present invention relates to the field of the pharmaceutical compositions and preparations (phytopreparations), or medical preparations in the form of compressed lozenges, gels, solutions and sprays with incorporated pulverized drug/herbal drugs extracts/essential oils from the lichen Usnea barbata - Old Man's Beard, Origanum heracleoticum - Greek oregano, Sideritis scardica - Mountain tea, Satureja montana - Winter savory, for treatment of the inflammation of mucous membranes of the mouth and throat, for the preventive and therapeutic purposes in human and veterinary medicine. Such a combination leads to reduction or elimination of symptoms of impaired soft tissues and stimulates regeneration of the mucous membrane of the mouth, pharynx, tongue and gums at: noninfectious and infectious acute and chronic inflammatory processes (gingivitis, stomatitis, aphthae, herpes lesions); irritations caused by tobacco smoke, the smaller injuries and burns; for prevention of periodontal disease and for strengthening the gums, as well. The present invention also relates to the process of preparing the already above mentioned pharmaceutical preparations. According to the International Patent Classification (IPC), the present invention belongs to the class: A 61K (9/06, 9/08, 9/66, 9/10, 9/12, 36/20) A 61P 31/00.

Background Art

Numerous scientific investigations have shown that medicinal plants contain biologically active classes of compounds (polyphenols, flavonoids, tannins, essential oils, mucus etc.) with different pharmacological activities and a real therapeutic actions ascribed. Due to the current trend of "way back to nature and its resources", application of medicinal plants as raw materials in pharmaceutical industry (herbal drugs), cosmetic industry (medicinal cosmetics) and food industry (dietetic supplements, functional foods) becomes important and a matter of interest.

Rational phyotherapy, based on the scientific basis and the application of high-quality, well defined, efficient and safe herbal remedies, have been assuming an increasingly important place in the modern phamacotherapy. Herbal preparations are gaining increasing importance in the prophylaxis and various diseases treatment, and, compared to synthetic medicines, with the main advantage in well-documented evidences on less of adverse effects. It was scientifically confirmed that a number of aromatic and medicinal plants containing biologically active substances with anti-inflammatory, antibacterial, astringent and similar actions could effectively reduce or eliminate a number of different symptoms caused by infection of the mucous membranes of the mouth and throat. Phytopreparations, containing specifically selected
herbal drugs, with biologically active ingredients exhibit a positive effect on the site of inflammation: antibiotic, antimicrobial, antiviral, emollient, anti-inflammatory, and astringent and thereby facilitate problems of impaired tissues and stimulate regeneration of the mucous membrane of the mouth, pharynx, tongue and gums. Synthetic mouth-care products (eg Hexoral solution - chlorhexidine gluconate as active principle), often in an enduring application can cause adverse side effects or lack of efficacy. Also, a vast number of natural products for this purpose contain substances of natural origin, but without a defined content of active principles. Taking into account that the morden medicine is nowadays faced with the problems of bacterial resistance to antibiotics, substances with antibacterial properties isolated from natural sources are in the focus of scientfic and practical view of interest.

Despite the large number of nowadays known antibiotics and chemotherapeutics on the world market (over 200 kinds, including 50 kinds of penicilllin, 70 kinds of cephalosporine and 20 kinds od quinolone), the problem of multiresistance of bacteria to antibiotics still persists. During 2001. only in the USA, 24,6 millions of kilograms of antibiotics has been produced for livestock production and veterinary medicine and about 3 millions of kilograms for application in human medicine. The consequence of this massive antibiotic production is increasing the antibiotic resistance of bacteria and appearance of panresistance phenomenon -resistance to all available antibiotics. Multiressistant strains are multiplied daily and they have inhabited farms, hospitals, schools and environment and cause severe, in most cases fatal infections worldwide in animals and humans. On the other hand, pharmaceutical industry did not develop any new so called „blockbuster” antibiotic for wide usage in human or veterinary clinical practice. There are several reasons for that: firstly, selective toxicity of many of the newest antimicrobials is too low, thus these new antimicrobials are not useful because of their high toxicity against host's cells. Secondly, clinical investigations of new antimicrobials are very expensive and time consuming. And finally, for the marketing of new products, years are needed after new product could become available for consumers. So, studies of antibacterial effect of non-antibiotical substances of different origin, including herbal extracts, are more present nowadays, with the objective to treat humans and animals in cases of infections induced by multiresistant strains of bacteria.

Previous research and empirical data regarding the biological and therapeutic properties of herbal active ingredients and their application represent the base for the appropriate selection of medicinal plants for phytopreparations, with favorable effect on the bacteria causing the inflammation of soft tissues of the mouth and pharynx. Complex biological active substances, ingredients of medicinal and aromatic plants such as essential oils, phenolic compounds, mucilage, minerals, enzymes and other secondary metabolites are responsible, in this specific case, for antiseptic action. The combined effects of active ingredients of our original compositions, cover a positive impact on the normal function of the soft tissues of the mouth and
throat, including a strong antiseptic effect as well, which is required in the treatment of hoarseness, laryngitis, pharyngitis, tonsillitis and inflammation and pain mitigation in throat.

In the phytopreparations, intended for use as topical preparations, the employed substrates does not represent the inert carrier of active ingredients or plants extracts. Composition and physico-chemical characteristics of the substrate affect the bioavailability of the active substances and their therapeutic effect; hence substrates/carriers should be carefully constructed regarding physical-chemical properties which would enable the appropriate phytopreparation application in the treatment of the inflammation of mouth mucous membranes and pharynx. Substrates should be compatible with active ingredients, stable, non-irritating, non-sensitizing and enable to provide the stability of the drugs and suitable pH value. Besides, the administration should be convenient and facilitated; the carrier should adhere well to the skin and mucous membranes and, possibly, contribute to prolonged action of the active principles on the application site.

Microbial and anti-inflammatory activity of herbal drugs *Usnea barbata* L., Parmeliaceae *Origanum heracleoticum* L., Lamiaceae, *Satureja montana* L., Lamiaceae, *Sideritis scardica* Griseb., Lamiaceae, are well-known, but the present patent claims combinations that have not been mentioned in the recent or earlier literature data.

1. *Usnea barbata* L., Parmeliaceae, Old Man's Beard

The lichen and its main active component, usnic acid, are traditionally used for medicinal and cosmetic purposes, as well as in homoeopathy. They have significant antibacterial, antiviral, antiproliferative antimicrobial, antiinflammatory, antipyretic and analgetic activity.

2. *Origanum heracleoticum* L., Lamiaceae, Greek Oregano

Herbal drug - *Origani heracleoticici herba* contains up to 3% essential oil and flavonoids. It has antimicrobial activity. It is used for treatment of the respiratory tract problems (cough, bronchitis), as well as for treatment of digestive and urinary tract disorders. It is widely used as spice.

Beside *O. heracleoticum*, the other species of the genus *Origanum*, such as *Origanum vulgare* L. are also widely used as antimicrobial and antifungal agents. Essential oil is considered to be the most responsible for biological activities due to presence of phenolic compounds (thymol, 11.6% and carvacrol, 3.5%). The essential oil (at concentrations less then 2%) inhibits growth of *Candida albicans*, *Aspergillus niger*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Streptococcus faecalis*, *Bacillus subtillis*. *O. vulgare* has antioxidant effects.

3. *Sideritis scardica* Griseb., Lamiaceae, Mountain Tea

Aerial parts at flowering stage (*Sideritis herba*) are used as a herbal drug. Aerial parts contain up to 0.6% essential oil, tannins, bitter substances, polyphenols, minerals, etc. Mountain
Tea has been used since old times in traditional medicine of Southern Europe. Decoct and infuse of Mountain tea are commonly consumed in Greece during the winter period. It is used for treatment of cough, respiratory tract disorders, anemia and gastritis. This tea is used for enjoying and is greatly appreciated for its pleasant odor and colour.

4. *Satureja montana* L., Lamiaceae, Winter Savory

   Aerial parts at flowering stage are used as herbal drug, *Saturejae montanae herb*. Herbal drug contains up to 2% essential oil (there are three chemotypes, carvacrol, thymol and linalool chemotype, among them carvacrol chemotype is the most appreciated), triterpenes, cinnamic acid derivatives, flavonoids. It is used as antiseptic, stomachic and carminative agent for its beneficial effect in treatment of inflammation of the urinary tract, respiratory and digestive systems, inflammation of skin and mucosa. Winter Savory is widely used as a spice in meat and fish dishes. It is greatly appreciated by people, especially in the regions where it is widely distributed; it is considered to possess wide spectrum of biological properties. It is also called a „Men's Tea“.

Herbal drugs may be used as active principles in different pharmaceutical compositions (tablets, capsules, creams, gels, fats, syrup, etc.). Compressed lozenges differ from conventional tablets in organoleptic properties; they disintegrate slower comparing to tablets and are less soluble. Disintegration process of lozenges obtained by compression of active substances and excipients is usually assisted by adding of small quantities of substances which promote decomposition process. Investigations were performed with numerous substances (starch, sodium starch glycolate, microcrystalline cellulose, sodium croscarmellose). The results have shown that the best effects were achieved with extragranular microcrystalline cellulose. Lozenges for the treatment of the soft tissues of the throat usually contain taste corrigents. Our formulations contain aroma of peppermint because of its characteristic taste and odor which masks the undesired aroma of active substances and at the same time reduces the sweetness of formulation (lozenges/solution/gel) as a consequence of a high quantity of sugar present.

   Mouthwashes are Water solutions for the treatment of the mucous membranes of the mouth. They are not supposed to be swallowed. They can be in a form of solutions or concentrated solutions which should be diluted before the use. Spray is a solution aimed for the dispersion within the oral cavity and has a local action. These solutions are packed into vessels with dispensing system, optionally under pressure and with possible dose regulation. Sprays should provide appropriate dimensions of drops for their localization in the mouth or throat.

   Gels for treatment of oral mucous membrane are described in the Sixth European Pharmacopoeia (Ph Eur 6.0) within the section Semi solid preparations for cutaneous use. Semi-
solid preparations for treatment of oral mucous membrane meet the requirements of the monography Semi-solid oromucosal preparations, for administration to the oral cavity or to the specific part of oral cavity.

Nowadays, there is a significant number of preparations based on the raw material/active principles of natural origin (extracts and essential oils from herbs) on the market, but without precisely defined antimicrobial potential.

GRANOBIL, (Grandel, Germany) PASTILES have been designed for mouth and throat infections, contains extract of *Usnea barbata* in concentration of 1.7%, dosed 1-2 PASTILE 3 to 4 times a day.

FITOSEPT (Zdravlje, Aktavis, Serbia) lozenges are designed on the basis of sodium usniate as an antimicrobial agent. The ones for adults contain 0.1 mg sodium usniate with 2 or 3 mg of menthol, while the ones for children are formulated with 0.05 mg of sodium usniate.

PASTILE ISLA contain 80 mg of water extract of *Cetraria islandica* and exist on the market as three products: with sugar (saccharose) - ISLA®-MOOS, with mint essential oil, sorbitol and aspartame - ISLA®-MINT, and with vitamine C, sorbitol and acesulfame - ISLA®-CASSIS.

TISAL® lozenges contain dry extract of linden flower.

SALVI PANTEN® lozenges have been formulated with dry extract of sage, vitamine C and panthenol.

PROTEKT BELI SLEZ® lozenges contain dry extract of marshmallow root (*Althaea officinalis*).

EKO SEPT® lozenges contain essential oil of sage and peppermint.

In the available Patent documents the following relevant documents were listed: Patent RS 49778 B titled "The pharmaceutical disinfectant product on the basis of sodium-usniate and medicinal herbs and the procedure for obtaining them" that protects pharmaceutical products based on sodium-usniate and medicinal herbs: sage or thyme or fennel or mint.

In EP 0256 566 entitled "Using usnic acid or its derivatives in the treatment of dental caries" usnic acid or its derivatives can be formulated into toothpaste, tooth powder, hygiene preparations for artificial dentures, chewing gum, toothpaste canal orifice and coatings for dental caries. Therefore, in the patent EP 0256 566, there are formulations for the treatment of dental caries, while in the present invention the subject of the protection is a pharmaceutical product based on extract of *Usnea barbata* with antimicrobial activity, intended for use in the case of inflammatory mucosa of the mouth and pharynx.

Application WO 00 03612 entitled "Antimicrobial compositions" states antimicrobial additives to increase shelf life and stabilize the microbial processes that are related to, among other, the pharmaceutical and cosmetic products and ingredients. In the present invention the
subject of the protection is a pharmaceutical product based on extract of *Usnea barbata*, not usnic acid. Also, *Usnea barbata* extract in the present invention is the active principle, not additive.

According to DE 23 54 517 entitled "Beauty Products", subject-matter is a cosmetic product for dermatological application based on the (+)-usnic acid, whereas in the present invention the aim is protecting pharmaceutical products for other purposes, which contains an extract of *Usnea barbata*, not (+)-usnic acid.

In the available patent and non-patent literature, it is not known composition, preparation or procedure for obtaining pharmaceutical products, reffered to our invention, based on pulverised herbal drugs, extracts and essential oils (*Usnea barbata*, *Origanum heracleoticum*, *Sideritis scardica*, *Satureja montana*) for therapeutic applications in the treatment of light to moderate bacterial and fungal infections of the mucosa of the mouth and throat.

**Disclosure of Invention**

The core of the invention is production of a pharmaceutical composition which contain selected and combined pulverized herbal drugs possessing antimicrobial properties (aerial parts of herbs: *Usnea barbata*, *Origanum heracleoticum*, *Sideritis scardica* and *Satureja montana*) and their isolates (extracts and essential oils). Selected combination of isolates/pulverized drugs is incorporated into a pharmaceutical composition (compressed lozenges, solution, gel, spray) in order to obtain efficient antimicrobial action of active herbal substances against the cause of infection in treatment of oral cavities infections and pharynx inflammation.

**Brief Description of Drawings**

Fig.1. HPLC chromatogram at $\lambda = 280 \text{ nm}$ of *Usnea barbatae extractum*, UB - extract according to the invention, isolated by supercritical carbon dioxide extraction with UV spectrum of indetified usnic acid. HPLC method was developed especially for this purpose.

Fig.2. HPLC Chromatogram of the extract from the Mountain Tea at $\lambda = 360$ and 280 nm with the spectra of identified compounds, compared to UV spectra of reference standards and chemical structures of identified compounds. Numbers refer to the following: protocatechuic acid (1), chlorogenic acid (2), vanillic acid (3), caffeic acid (4), syringic acid (5), *p*-coumaric acid (6), ferulic acid (7), luteolin-7-O-glycoside (8), apigenin-7-O-glycoside (9), luteolin (10), chrysoeriol (11) and apiogenin (12).

**Best Modes for Carrying Out of the Invention**

The core of the invention is combination of the most effective plants, technology of the extract production, formulations and technology of production of phyto preparations based on pulverized herbal drugs, plant extracts and essential oils for treatments of inflammation of oral
mucous membranes of the mouth and pharynx. Thereby, the application of the pharmaceutical composition in phytopreparations of different pharmaceutical forms (compressed lozenges, solution, spray, gel) enables efficient action of all the components and the best effect.

The invention describes composition of plant raw materials, production of plant extracts, formulations and processes for production of compressed lozenges, gel and solution with the best effects in action against pathogens of oral cavity and throat. Applicability of the composition is based on the scientifically proven biological properties of the active components. Although the medicinal properties of the active principles of selected herbs individually are known to the great extent from traditional use and lately scientifically proven, the proposed combination is new and original. Extracts of Greek oregano, Mountain tea and Winter savory are added to the most active extract of Usnea lichen.

Extracts, essential oils, and pulverized material were produced from the selected herbs: Usnea barbata, Origanum heracleoticum, Sideritis scardica and Satureja montana, in order to make formulations and produce phytopreparations.

According to the invention, phytopreparations comprise:

- extracts of the lichen Usnea barbata isolated by the process of supercritical fluid extraction:
  a) Commercial extract of the lichen Usnea barbata (Flavex, Germany) obtained by supercritical carbon dioxide extraction with posterior purification of the extract in order to increase usnic acid content to 80-90% mass.

b) The extract of the lichen Usnea barbata collected in F.Y.R. Macedonia isolated by supercritical carbon dioxide extraction (from now on referred to as "UB - extract according to the invention"). Supercritical carbon dioxide extraction was performed in the laboratory scale unit for supercritical fluid extraction, Autoclave Engineers SCE Screening System at temperature of 40 °C and at pressure of 30 MPa. The extraction yield of 0.6% was achieved.

HPLC chromatogram of the extract is presented in Fig. 1.

dry extracts and/or pulveres and/or essential oils of the herbs Sideritis scardica, Satureja montana and Origanum heracleoticum are isolated by continuous extraction using Soxhlet apparatus and/or by standardized methods for diminution of herbal drugs and/or by hydrodistillation. The extraction yields were: 6.7% for S. montana, higher than 15.3% for O. heracleoticum and up to 16.7% for S. scardica. Chemical characterization of the extracts according to the invention is presented in Table 1, Table 2 and Fig.2.

The essential oils from the dried and ground aerial parts of the herbs Origanum heracleoticum, Sideritis scardica and Satureja montana, were isolated by steam distillation using a Clevenger-type apparatus. Air-dried aerial parts of Usnea barbata and aerial parts in the flowering stage of herbs Origanum heracleoticum, Sideritis scardica and Satureja montana were grounded in the mill and sieved using laboratory sieves (mesh sizes from 0.15 mm to 0.30 mm).
Pulveres were stored in the well-closed glass vessels and carried into a cold place protected from the sunlight.

Table 1. Content of the essential oil, total flavonoid content and tannins in the tested extracts

<table>
<thead>
<tr>
<th>Extracts/Herbal drug</th>
<th>Essential oil content (%)</th>
<th>Total flavonoid content (%)</th>
<th>Total tannins content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sideritis scardica</td>
<td>0.04</td>
<td>0.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Satureja montanae</td>
<td>0.15</td>
<td>0.11</td>
<td>0.94</td>
</tr>
<tr>
<td>Origanum heracleoticum</td>
<td>0.03</td>
<td>0.28</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Substances identified in HPLC Chromatogram of the extract from the Mountain Tea at λ = 360 and 280 nm (Fig.2.)

<table>
<thead>
<tr>
<th>No</th>
<th>Common name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Protocateheic acid</td>
</tr>
<tr>
<td>2</td>
<td>Hlorochlorogenic acid</td>
</tr>
<tr>
<td>3</td>
<td>Vanillic acid</td>
</tr>
<tr>
<td>4</td>
<td>Caffic acid</td>
</tr>
<tr>
<td>5</td>
<td>Siringic acid</td>
</tr>
<tr>
<td>6</td>
<td>p-kumarinska kiselina</td>
</tr>
<tr>
<td>7</td>
<td>Ferulic acid</td>
</tr>
<tr>
<td>8</td>
<td>Luteolin-7-O-β-glucoside</td>
</tr>
<tr>
<td>9</td>
<td>Apigenin-7-O-β- glucoside</td>
</tr>
<tr>
<td>10</td>
<td>Luteolin</td>
</tr>
<tr>
<td>11</td>
<td>Chrysoeriol</td>
</tr>
<tr>
<td>12</td>
<td>Apigenen</td>
</tr>
</tbody>
</table>

Antibacterial activity of plant extracts contained in formulations of the invention are presented in tables 2, 3, 4 and 5. The extracts of Usnea barbata showed strong antibacterial activity with MIC (Minimal inhibitory concentration) values from 5-40 μg/mL (Table 3).

Table 3. Results of the investigation of antibacterial activity of the lichen extracts

<table>
<thead>
<tr>
<th>Bacterial species and strain</th>
<th>UB*</th>
<th>UB Flavex</th>
<th>Gentamicin (Sigma)</th>
<th>Ampicillin (Sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus ATCC 25923</td>
<td>40</td>
<td>40</td>
<td>&lt;0,5</td>
<td>0,5</td>
</tr>
</tbody>
</table>
Staphylococcus aureus, 1
Staphylococcus aureus, 2
Methicillin-resistant S. aureus (MRSA) ATCC 43300
Streptococcus agalactiae, ATCC 27956
Streptococcus pyogenes, 1
Streptococcus pyogenes, 2
Enterococcus faecalis

* - UB - extract according to the invention

The Mountain tea extract (SD) had moderately strong antibacterial activity against

*Corynebacterium pseudotuberculosis.* Tested extract showed moderately strong to very strong antibacterial activity against some gram-negatives (Pasteurella multocida, Haemophilus sp.) with obtained MIC values of 40-320 µg/mL (Table 4).

Table 4. Results of the investigation of antibacterial activity of the Mountain tea extract

<table>
<thead>
<tr>
<th>Bacterial species and strain</th>
<th>SD</th>
<th>Gentamicin (Sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (µg/mL)</td>
<td></td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>320</td>
<td>&lt;0,5</td>
</tr>
<tr>
<td><em>Haemophilus sp.</em></td>
<td>40</td>
<td>&lt;0,5</td>
</tr>
<tr>
<td><em>Corynebacterium pseudotuberculosis</em></td>
<td>320</td>
<td>&lt;0,5</td>
</tr>
</tbody>
</table>

The Greek oregano extract (OH) showed moderately strong activity against most of the investigated gram-positives and gram-negatives with obtained MIC values from 80-320 µg/mL (Table 5).

The Winter savory extract (SAT) showed moderately strong to very strong antibacterial activity against *Corynebacterium tuberculosis* and some gram-negatives (Pasteurella multocida, Haemophilus sp.) with obtained MIC values of 80-640 µg/mL (Table 6). Table 7 shows antibacterial activity of the combination of extracts which was used in formulations of this invention.
Table 5. Results of the investigation of antibacterial activity of the Greek oregano extract

<table>
<thead>
<tr>
<th>Bacterial species and strain</th>
<th>OH MIC (µg/mL)</th>
<th>Gentamicin (Sigma)</th>
<th>Ampicillin (Sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pyogenes</em> 1</td>
<td>320</td>
<td>-</td>
<td>0,125</td>
</tr>
<tr>
<td><em>Streptococcus canis</em></td>
<td>640</td>
<td>-</td>
<td>0,5</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> 2</td>
<td>80</td>
<td>-</td>
<td>0,125</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>320</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>320</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>MRSA ATCC 43300</td>
<td>160</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td><em>Corynebacterium pseudotuberculosis</em></td>
<td>160</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>160</td>
<td>&lt;0,5</td>
<td>-</td>
</tr>
<tr>
<td><em>Haemophilus sp.</em></td>
<td>320</td>
<td>&lt;0,5</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6. Results of the investigation of antibacterial activity of the winter savory extract

<table>
<thead>
<tr>
<th>Bacterial species and strain</th>
<th>SAT MIC (µg/mL)</th>
<th>Gentamicin (Sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>320</td>
<td>&lt;0,5</td>
</tr>
<tr>
<td><em>Haemophilus sp.</em></td>
<td>80</td>
<td>&lt;0,5</td>
</tr>
<tr>
<td><em>Corynebacterium pseudotuberculosis</em></td>
<td>640</td>
<td>&lt;0,5</td>
</tr>
</tbody>
</table>

Table 7. Antimicrobial activity of the combination of extracts

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>Combination of extracts</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pyogenes</em> 1</td>
<td>80</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> 2</td>
<td>80</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>160</td>
</tr>
<tr>
<td><em>Staph. aureus ATCC 25923</em></td>
<td>320</td>
</tr>
<tr>
<td><em>Staph. aureus</em> clinical isolate</td>
<td>320</td>
</tr>
<tr>
<td>MRSA ATCC 43300</td>
<td>320</td>
</tr>
<tr>
<td>MRSA ATCC 33591</td>
<td>320</td>
</tr>
<tr>
<td>MRSA clinical isolate</td>
<td>320</td>
</tr>
<tr>
<td><em>E.coli ATCC 25922</em></td>
<td>2560</td>
</tr>
<tr>
<td><em>E.coli</em> clinical isolate</td>
<td>2560</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> clinical isolate</td>
<td>2560</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> clinical isolate</td>
<td>2560</td>
</tr>
<tr>
<td><em>Corynebacterium pseudotuberculosis</em> clinical isolate</td>
<td>160</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> clinical isolate</td>
<td>80</td>
</tr>
</tbody>
</table>
Although the extracts mixture showed good antibacterial activity against gram-positive bacteria, it has showed weak or no activity against gram-negative species, especially the members of Enterobacteriaceae family. This indicates that usage of this mixture will have no adverse effect on normal gastrointestinal flora of consumers.

Compressed lozenges that contain the combination of extracts showed antibacterial activity against S.pyogenes and S.aureus strains, including Methicillin resistant Saphylococcus aureus (MRSA) strains. According to the disc diffusion method, compressed lozenges showed antibacterial activity with 18-20 mm inhibition zones on the plates inoculated with investigated strains suspensions of 100 000 CFU/ml compared to clindamycin discs with 20-22 mm zones, and 25-30 mm inhibition zones of oriblettes on the plates inoculated with 10 000 CFU/ml, compared to clindamycin discs with 24 to 36 mm inhibition zones.

According to the broth macrodilution method, the compressed lozenges showed good antibacterial activity in the medium with bacterial concentrations of 100 000 and 10 000 CFU/ml, i.e. the total number of bacteria after the incubation was reduced 10 times, compared to controls without oriblettes in which number of bacteria has increased to the level where the proper counting was impossible. The number of 100 000 and 10 000 CFU/ml is not minor, on the contrary for the most microorganisms it is equal to infection dose.

The present invention provides the following pharmaceutical formulations: lozenges, solutions, gels and sprays.

Compressed lozenges according to the present invention include:

a. pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, Satureja montana L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, Sideritis scardica Griseb., Lamiaceae in the range 0.10 to 0.70% by weight.

Preferably, extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form and satisfactory product texture, the usual pharmaceutical excipients have been employed.

b. pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

c. pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano,
**Origanum heracleoticum** L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae, in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

d. pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

**Gels according to the present invention include:**

a) pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

b) pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

c) pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

d) pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano,
Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, Satureja montana L., Lamiaceae, in the range 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

Solutions, according to the present invention include:

a) herbal extracts / essential oils of lichen Old Man’s Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, Satureja montana L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, Sideritis scardica Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

b) herbal extracts / essential oils of lichen Old Man’s Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, Sideritis scardica Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

c) herbal extracts / essential oils of lichen Old Man’s Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, Sideritis scardica Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

d) herbal extracts / essential oils of lichen Old Man’s Beard, Usnea barbata L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, Origanum heracleoticum L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, Satureja montana L., Lamiaceae, in the range 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

Sprays, according to the present invention include:
a) herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight.

Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

b) herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

c) herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

d) herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight. Preferably extracts based on a water-ethanol-basis are used, as well as the extract obtained by supercritical fluid extraction. In order to obtain the proper dosage form, and satisfactory product texture the usual pharmaceutical excipients have been employed.

The present invention will be demonstrated through the following examples which do not constrain the invention:

**Example 1.**

**Obtaining lichen extract by supercritical fluid extraction**

Lichen is milled and sieved. Fraction caught between sieves of 0.2 and 0.6 mm is used for the extraction. 30 grams of milled and sieved lichen is placed in a 150 cm³ extractor. After reaching
the operating conditions (pressure and temperature), a continuous flow of supercritical fluid (0.5 kg/h) is established. Substances dissolved in the supercritical fluid are collected in the separator vessel due to the reduction of pressure. Extraction lasts until the raw material is exhausted.

Specific consumption of supercritical carbon dioxide is 24 grams of carbon dioxide per gram of lichen.

Obtaining extracts by continuous extraction in Soxhlet-apparatus

Solvent: Ethanol 70% (v/v)

a) 50 g of drug is comminuted and put in two paper tubes (20.00 g each, accurately weighed)
b) Ethanol is pored over the drug (70%, v/v) in the amount of 2 1/2-volume of Soxhlet, so that the paper tube is soaked with solvent. It si left over night.
c) Turn on the water supply to the condenser and turn on the heaters to 5 until the solvent boils, then reduce to 3 or 4. Extract until bleaching.
d) After extraction turn the power off, leave the water until the solvent is completely cooled, transfer the extract into a glass, and rinse the extraction balloon with ethanol (70%, v/v) (3 x 10 ml)
e) Measure a tare of a balloon of 50 ml and evaporate the ethanol from extract in a vacuum evaporator
f) Leave the balloon with extract in an oven at 30 °C to dry the extract
g) Measure the mass of the balloon with the extract

Obtaining essential oils by hydrodistillation

200 g of plant material (Sideritis scardica, Satureja montana and Origanum heracleoticwri) is subjected to hydrodistillation in the Clevenger apparatus with the essential oil yield of 0.01 to 3.5%.

Example 2.

Production of compressed lozenges that contain combination (two, three or four) of plant extracts/essential oils

Wet granulation: Solution of binding matter is made by its dispensing (0.3-0.57 kg) over the surface of distilled water (0.1-0.77 kg) with posterior swelling during 10-25 minutes. Binding matter is dissolved after swelling by mixing at 700-1500 rpm. in the next 10-25 minutes.

Mixing of powders is performed in a mixing vessel for high shear velocities during 20 minutes at 700 rpm: glucose monohydrate (1.50-2.15 kg); the extracts: Old Man's Beard lichen (Usnea barbata) in the range of 0.001-0.03 %, Greek oregano (Origanum heracleoticum) in the range of 0.10-0.50 %, mountain tea (Sideritis scardica) in the range of 0.10-0.70% and winter savory (Satureja montana) in the range of 0.10-0.50% as well as saccharose (1.50-3.40 kg). Granulation of the obtained mass is
performed in a rotary granulator through the sieve of 2 mm with posterior drying in a drying chamber at 50°C until the humidity of the granular material is in the range 1-2% is achieved. Dried granular material is further sieved in a oscillating granulator through the sieve of 0.8 mm.

Production of mass for tableting process: Microcrystalline cellulose pH 101 (015-0,41 kg) is added to the granular material as well as aroma of peppermint (0,01-0,1 kg) with posterior mixing during 5-15 minutes. At the end, magnesium stearate (0,01-0,05 kg) is added to the mass and mixing is continued in the next 1-10 minutes.

Tableting process: Previously prepared tableting mass is introduced into a rotary tableting machine. Round compressed lozenges/tablets, white with smooth surfaces are obtained with characteristics as follows:

Calculated mass of tablet: 1.1000 g

Tolerance:
- from the mass of a tablet: ±5% (1,0450 g - 1,1550 g)
- from the average mass: ±3% (1,0670 g - 1,1330 g)

Diameter: 15 mm
Thickness: 3,30-3,50 mm
Firmness: 8-15 kp
Friability: max. 1%
Drying loss: 1,5-2,5%.

Example 3.
Procedure for obtaining solution containing combination of (two, three or four) plant extracts or essential oils

Solution on the basis of extracts or essential oils from *Usnea barbata*- Old Man’s Beard lichen, *Origanum heracleoticum*-Greek Oregano, *Sideritis scardica*- Mountain Tea, *Satureja montana*-Winter Savory which contain active principles, is used for treatment of inflammation of the oral and pharyngeal mucosa. The solution contains: ethanol 10.0-70.0 g, water 30.0-80.0 g, propileneglycol 40.0-50.0 g and polysorbate 2.0 - 5.0 g.

Dried extracts of Old Man’s Beard lichen (*Usnea barbata*) in the range of 0.00 1-0.03%, aerial parts of Greek Oregano (*Origanum heracleoticum*) in the range of 0.10-0.50%, aerial parts of Mountain Tea (*Sideritis scardica*) in the range of 0.10-0.70% and aerial parts of Winter Savory (*Satureja montana*) are added into solution (ethanol, water, propileneglycol, polysorbate) and stirred with the propeller mixer at 500-700 rpm, to form a homegeneuos solution.

Example 4.
Procedure for obtaining gel containing combination of (two, three or four) plant extracts or essential oils

A semi-solid product, gel obtained according to the suggested formulation i.e. suggested composition (active component and carrier) fulfills all prescribed requirements for the local application.

Extracts: Old Man’s Beard lichen (*Usnea barbata*) in the range of 0.001-0.03%, aerial parts of Greek Oregano (*Origanum heracleoticum*) in the range of 0.10-0.50%, aerial parts of Mountain Tea (*Sideritis scardica*) in the range of 0.10-0.70% and aerial parts of Winter Savory (*Satureja montana*) are dissolved in the mixture of water (50-85%) and ethanol (5-15%) and sirred with the propeller mixer at 500-700 rpm. After dissolution, 0.5-1.2% of the gelling agent (carbomer) is sprinkled on the surface. After swelling (15 min) and stirring (at the same rate, 15 min) the gelling agent is added (10% solution of sodium hydroxide). Formed gel is homogenized (700 rpm) and left at ambient temperature for 24 h until complete structuring of the system.

Example 5.

Procedure for obtaining spray containing combination of (two, three or four) plant extracts or oils

Solution for spray on the basis of extracts and essential oils from *Usnea barbata*- Old Man’s Beard lichen, *Origanum heracleoticum*-Greek Oregano, *Sideritis scardica*- Mountain Tea, *Satureja montana*-Winter Savory, which contain active principles, is used for treatment of inflammation of the oral and pharyngeal mucosa and it contains: ethanol 10.0-70.0%, purified water 30.0-80.0 %, propileneglycol 40.0-50.0% and polysorbate20 in the range of 2.0 - 5.0 %.

Dried extracts of Old Man’s Beard lichen (*Usnea barbata*) in the range of 0.001-0.03%, aerial parts of Greek Oregano (*Origanum heracleoticum*) in the range of 0.10-0.50%, aerial parts of Mountain Tea (*Sideritis scardica*) in the range of 0.10-0.70% and aerial parts of Winter Savory (*Satureja montana*) are added into solution (ethanol, water, propileneglycol, polysorbate) and stirred with propeller mixer at 500-700 rpm, to form homogeneuos solution which is further placed in the glass bottles with the mechanical pump.

**Industrial Applicability**

The present invention is phytopreparation in the form of compressed lozenges, gels, solutions and sprays with incorporated pulverized drug/herbal drugs extracts/essential oils from the lichen *Usnea barbata* - Old Man’s Beard, *Origanum heracleoticum* - Greek oregano, *Sideritis scardica* - Mountain tea, *Satureja montana* - Winter savory, for the application in treatment of the inflammation of mucous membranes of the mouth and throat, as well as for the preventive and therapeutic purposes in human and veterinary medicine. Application of proposed phytopreparation leads to reduction or elimination of symptoms of impaired soft tissues and stimulates regeneration of the mucous membrane of the mouth, pharynx, tongue and gums at: noninfectious and infectious acute and chronic inflammatory processes (gingivitis, stomatitis,
aphtae, herpes lesions); irritations caused by tobacco smoke, the smaller injuries and burns; for prevention of periodontal disease and for strengthening the gums, as well.
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CLAIMS


2. The pharmaceutical preparation according to patent claim 1, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

3. The pharmaceutical preparation according to patent claim 1, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

4. The pharmaceutical preparation according to patent claim 1, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

5. The pharmaceutical preparation according to patent claim 1, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

6. The method of producing the compressed lozenge according to patent claim 2, wherein the solvent polyvinylpyrrolidone (PVP K-25) is mixed with glucose, then with extracts /
herbal pulvis trituratore and sucrose, as well, in order to perform the process of granulation. The obtained granules dried to moisture content of 0.5-5%.

The next step compromises cooling and addition of pulverized drug / herbal extracts / essential oils of Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. After that, subject the obtained granules to drying to max. 10% moisture content. The last stage before obtaining lozenges from the prepared granules is addition the corresponding lubricant.

7. The method of producing the compressed lozenge according to patent claim 3, wherein the solvent polyvinylpyrrolidone (PVP K-25) is mixed with glucose, then with extracts / herbal pulvis trituratore and sucrose, as well, in order to perform the process of granulation. The obtained granules dried to moisture content of 0.5-5%. The next step compromises cooling and addition of essential oils of Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, After that, subject the obtained granules to drying to max. 10% moisture content. The last stage before obtaining lozenges from the prepared granules is addition the corresponding lubricant.

8. The method of producing the compressed lozenge according to patent claim 4, wherein the solvent polyvinylpyrrolidone (PVP K-25) is mixed with glucose, then with extracts / herbal pulvis trituratore and sucrose, as well, in order to perform the process of granulation. The obtained granules dried to moisture content of 0.5-5%. The next step compromises cooling and addition of pulverized drug / herbal extracts / essential oils of Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight. After that, subject the obtained granules to drying to max. 10% moisture content. The last stage before obtaining lozenges from the prepared granules is addition the corresponding lubricant.

9. The method of producing the compressed lozenge according to patent claim 5, wherein the solvent polyvinylpyrrolidone (PVP K-25) is mixed with glucose, then with extracts / herbal pulvis trituratore and sucrose, as well, in order to perform the process of granulation. The obtained granules dried to moisture content of 0.5-5%. The next step compromises cooling and addition of pulverized drug / herbal extracts / essential oils of Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight. After that, subject the obtained granules to drying to max. 10% moisture content. The last
stage before obtaining lozenges from the prepared granules is addition the corresponding lubricant.

10. The pharmaceutical preparation in gel form according to patent claim 2, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man’s Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heradeoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

11. The pharmaceutical preparation in gel form according to patent claim 3, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man’s Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight and Greek oregano, *Origanum heradeoticum* L., Lamiaceae, 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

12. The pharmaceutical preparation in gel form according to patent claim 4, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man’s Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heradeoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

13. The pharmaceutical preparation in gel form according to patent claim 5, wherein consisting of pulverized drug / herbal extracts / essential oils of lichen Old Man’s Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heradeoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

14. The pharmaceutical preparation in the form of a solution according to patent claim 2, wherein consisting of herbal extracts / essential oils of lichen Old Man’s Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heradeoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the
addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

15. The pharmaceutical preparation in the form of a solution according to patent claim 3, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight and Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

16. The pharmaceutical preparation in the form of a solution according to patent claim 4, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

17. The pharmaceutical preparation in the form of a solution according to patent claim 5, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

18. The pharmaceutical preparation in the form of a spray according to patent claim 2, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

19. The pharmaceutical preparation in the form of a spray according to patent claim 3, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, and Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.
20. The pharmaceutical preparation in the form of a spray according to patent claim 4, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Mountain tea, *Sideritis scardica* Griseb., Lamiaceae in the range 0.10 to 0.70% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

21. The pharmaceutical preparation in the form of a spray according to patent claim 5, wherein consisting of herbal extracts / essential oils of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, in the range of 0.001 to 0.03% by weight, Greek oregano, *Origanum heracleoticum* L., Lamiaceae, 0.10 to 0.50% by weight, and Winter savory, *Satureja montana* L., Lamiaceae, in the range 0.10 to 0.50% by weight, with the addition of the usual pharmaceutical excipients in order to yield appropriate pharmaceutical preparation.

22. The extracts of lichen Old Man's Beard, *Usnea barbata* L., Parmeliaceae, wherein the supercritical fluid and continuous extraction, applying the SOHxLETapparatus using 70% ethanol (v/v) are performed, and as needed repeated, to afford extracts with 30 - 95% of total usnic acid content.

23. Extract of Greek oregano (*Origanum heracleoticum* L., Lamiaceae) wherein characterized by the essential oil content from 0.01 to 0.05% and 0.10-1.0% of total flavonoids.

24. Extract of Winter savory (*Satureja montana* L., Lamiaceae), wherein characterized by the essential oil content from 0.01 to 0.05%, 0.10-1.0% of total flavonoids and 0.1-2% of the total tannins.

25. Extract of Mountain tea (*Sideritis scardica* Griseb., Lamiaceae) wherein characterized by the essential oil content from 0.01 to 0.05%, 0.10-1.0% of total flavonoids and 3-10% of total tannins.

26. The pharmaceutical preparations according to the claims of 2-21 for use in inflammation of soft tissues of mouth and throat in human and veterinary medicine.
**INTERNATIONAL SEARCH REPORT**

**PCT/RS2012/000017**

### A. CLASSIFICATION OF SUBJECT MATTER

**INV. A61K36/09 A61K36/53 A61P29/00**

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K  A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

X See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed

**Date of the actual completion of the international search**

22 April 2013

**Date of mailing of the international search report**

04/06/2013

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax. (+31-70) 340-3016

Authorized officer

Thalmai r-De Meyere

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