

Herbal medicinal products in RESPIRATORY diseases

– STANce of the Polish PHYTOtherapy Association

– STANPHYTO RESPIRATORY I

ZBIGNIEW DONIEC^{1, 2, A, B, D-F}, MIROSŁAWA KRAUZE-BARANOWSKA^{3, A, B, D-F},

ORCID ID: 0000-0003-3896-1053

ORCID ID: 0000-0002-0344-7401

MIECZYŚLAWA CZERWIONKA-SZAFLARSKA^{4, B, D, F}, ERNEST KUCHAR^{5, B, D, F}, IZABELA FECKA^{6, A, B, D-F},

ORCID ID: 0000-0001-8170-308X

ORCID ID: 0000-0002-7883-2427

ORCID ID: 0000-0002-1139-4581

ADAM SYBILSKI^{7, 8, B, D, F}, JAROSŁAW WOROŃ^{9, B, D, F}, AGNIESZKA MASTALERZ-MIGAS^{10, B, D, F}

ORCID ID: 0000-0003-2389-277X

ORCID ID: 0000-0003-3688-1877

ORCID ID: 000-0001-6600-2760

¹ Pneumology Department, Institute of Tuberculosis and Lung Diseases, Field Branch, Rabka-Zdroj, Poland

² Medical Institute, Podhale State College of Applied Science, Nowy Targ, Poland

³ Department of Pharmacognosy, Medical University of Gdansk, Poland

⁴ A. Jurasz University Hospital, Department of Paediatrics, Allergology and Gastroenterology Clinic, Bydgoszcz, Poland

⁵ Department of Paediatrics and Observation Unit, Medical University of Warsaw, Poland

⁶ Department of Pharmacognosy and Herbal Medicines, Medical University of Wrocław, Poland

⁷ Department of Paediatric and Neonatal Diseases, National Medical Institute of the Ministry of Internal Affairs and Administration in Warsaw, Poland

⁸ Department of Paediatrics II, Postgraduate Medical Education Center, Warsaw, Poland

⁹ Department of Clinical Pharmacology, Jagiellonian University, Collegium Medicum of Cracow, Poland

¹⁰ Chair and Department of Family Practice, Medical University of Wrocław, Poland

A – Study Design, B – Data Collection, C – Statistical Analysis, D – Data Interpretation, E – Manuscript Preparation, F – Literature Search, G – Funds Collection

Summary Acute respiratory infections are the most common reason to seek medical attention in primary care. The infections are mostly of viral aetiology, and preparations containing herbal substances are used in symptomatic treatment. This paper reviews single and combination herbal medicinal products used for dry and wet (nonproductive and productive) cough. The therapeutic effects of individual herbal substances are discussed regarding the presence of specific biologically active compounds, taking into account the results of clinical and application studies.

Key words: respiratory tract infections, phytotherapy, plant preparations.

Doniec Z, Krauze-Baranowska M, Czerwionka-Szaflarska M, Kuchar E, Fecka I, Sybilski A, Woroń J, Mastalerz-Migas A. Herbal medicinal products in RESPIRATORY diseases – STANce of the Polish PHYTOtherapy Association – STANPHYTO RESPIRATORY I. *Fam Med Prim Care Rev* 2023; 25(3): 331–338, doi: <https://doi.org/10.5114/fmpcr.2023.131270>.

Background

Respiratory diseases in primary care practice mainly refer to acute Airway Respiratory Infections (ARIs), classified as either Upper Respiratory Infections (URIs) or Lower Respiratory Infections (LRIs). The most common acute infectious diseases include infections of the upper respiratory tract: acute nasopharyngitis (common cold), acute rhinosinusitis, acute otitis media, acute pharyngitis and tonsillitis, epiglottitis and laryngitis. The vast majority of URIs are of viral aetiology. Rhinoviruses account for 25–30% of URIs; RSV, parainfluenza, influenza viruses, human metapneumoviruses and adenoviruses account for 25–35%; coronaviruses for 10%; and unidentified viruses for the remaining percentage of infections [1]. The vast majority of URIs are benign and self-limiting; however, the complications of these infections, such as bacterial infections of the sinuses and middle ear, bronchi and lungs, may constitute a problem [2].

The inflammatory response to viral infection is a complex process involving innate and adaptive response mechanisms of the immune system. In the first stage of inflammation, as

a result of the release of mediators, such as histamine, prostaglandins and leukotrienes, local congestion occurs, as well as increased vascular permeability and swelling of mucous membranes. Local symptoms develop, such as hoarseness, sore throat, excess serous-mucous discharge from the nose, sneezing, dry cough and even shortness of breath. The second stage of inflammation involves infiltration of the respiratory tract by inflammatory cells, which release mediators that intensify the inflammatory process. The amount of secretion in the respiratory tract increases, and its physicochemical properties also change – becoming more viscous and thick. The physiological mechanisms of bronchial cleansing, such as coughing and the mucociliary apparatus, are disturbed. The patency of the bronchi is impaired, and there is an excess of thick secretion. Clinically, a gradual intensification of cough symptoms is observed, which changes from an initially dry cough to a productive and wet cough. These symptoms are usually accompanied by malaise, weakness, fever and muscle pain [3, 4]. In normal conditions, the body's inflammatory response, allowing for elimination of a pathogen, is gradually suppressed, and the symptoms of the disease subside within 1–2 weeks.



Since there are no effective medicines with an appropriate antiviral activity (except for oseltamivir, applied in the treatment of influenza), symptomatic medicines play a fundamental role in the treatment of respiratory tract infections. The initial dry cough (non-productive, without sputum) is an indication to apply treatment aimed at reduction of the severity of symptoms, as well as antitussive medications in case of their significant intensification. In the second phase of inflammation, which is dominated by wet cough (productive cough, with sputum), it is recommended to administer mucoactive medications (mucolytic, mucokinetic and expectorant) that improve the physiological mechanisms of bronchial clearance [3, 5]. In order to ensure effectiveness of these medicines, adequate hydration of the patients is of crucial importance. Improvement of bronchial patency and liquefaction of thick secretion residing in the respiratory tracts also reduce the risk of bacterial superinfections and, in case of necessary antibiotic therapy, increase its effectiveness.

Understanding the pathomechanisms of the inflammatory response also stresses the need to apply medications that not only alleviate strenuous symptoms triggered by a pathogen but which also have properties that support the effector mechanisms of the immune system. As a result, it is possible to reduce the severity of the symptoms of a disease, as well as to shorten its duration and lower the risk of related complications.

Herbal medicines in respiratory disease

A **herbal medicinal product** (commonly referred to as a herbal medicine) is a product containing, as an active ingredient or active ingredients, one or more herbal substances or one or more herbal preparations or their combinations. Herbal substances (formerly known as plant raw material) used in respiratory tract diseases are precisely defined by a part of the plant that is used, as well as its botanical name, and they exhibit the following properties:

- a) antitussive, protecting (coating) the upper respiratory tract mucosa,
- b) expectorant (secretolytic),
- c) mucolytic,
- d) mucokinetic,
- e) broncholytic,
- f) anti-inflammatory,
- g) antioxidant,
- h) immunomodulatory,
- i) antipyretic,
- j) diaphoretic,
- k) antiseptic (antimicrobial),
- l) other specified for a given substance, e.g. diuretic.

The spectrum of pharmacological activity of individual herbal medicines is usually much wider than that of synthetic medicines that are based on the “key-lock” principle. Due to the complex chemical composition of herbal substances and herbal preparations, in which the main biologically active constituents are accompanied by compounds of varied chemical structures affecting the human body in a different yet positive manner, many marketed herbal medicinal products, apart from their main scope of indications, i.e. symptomatic treatment, are characterised by additional biological properties. These are actions that positively affect the course of therapy, e.g. by limiting the growth and multiplication of pathogenic microorganisms, reducing inflammatory condition and oxidative stress (at least locally) and improving the functions of the immune system. This multidirectional effect of herbal medicines with more than one molecular target (also referred to as multi-targeted or multi-functional) is detailed in the EMA/HMPC monographs. Moreover, it should be stressed that the rational use of herbal medicinal products ensures safe and effective therapy and carries a lower risk of side effects (e.g. in the case of hypersensitivity to active substances and/or to any of the excipients) compared to other types of medications. For most of these, there are no known cases of overdose. However, due to insufficient data,

their use during pregnancy and breast feeding is not recommended. Non-clinical data does not reveal any particular hazard for patients based on safety pharmacology and toxicology studies, as well as evaluations of acute toxicity, repeated dose toxicity, genotoxicity and toxic effects on reproduction and development of offspring.

Medicinal products containing herbal substances are usually available as over-the-counter (OTC) medications, but the fairly common practice of “self-treatment” also makes patients reach for non-drug herbal dietary supplements (or dietary supplements containing active herbal substances). This has an impact on the effectiveness of treatment and also raises a number of questions both to doctors and pharmacists regarding the safety of their use. Thus, it now appears crucial for physicians to possess knowledge that would enable them to rationally apply herbal medicines based on their proven efficacy and safety in studies conducted in accordance with the criteria of Evidence Based Medicine (EBM). Importantly, this knowledge should be supplemented by familiarising doctors with the basic legal regulations on herbal product trading in Poland and EU.

In order to support harmonisation on the European market, the Committee on Herbal Medicinal Products (HMPC), which is a body of the European Medicines Agency (EMA), is responsible for the collection and evaluation of scientific data regarding herbal substances, herbal preparations and their combinations. Considering the requirements for safety and effectiveness of medical use, herbal substances and herbal preparations (referred to as herbal active substances) and herbal medicinal products that are made from them may be registered as traditional, of well-established use or in a mixed procedure [6]. In the case of well-established herbal medicinal products, scientific literature confirms that the substances and/or herbal preparations used for their production have well-established medical use with confirmed effectiveness and an acceptable level of safety, considering a period of at least 10 years from the first systematic and documented use of this substance in a medicinal product. Traditional use (simplified registration) means that although there is no sufficient clinical trial evidence, the effectiveness of these medicines has been confirmed based on long-term use and experience in medicine (over a period of at least 30 years, including at least 15 years in an EU Member State) and that there is sufficient data, particularly on safety when used as intended [6].

Herbal medicines, similarly to synthetic medicines, are available on the Polish pharmaceutical market after meeting the specific legal conditions for marketing authorisation by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (www.urpl.gov.pl), and their details are available in the Summary of Product Characteristics (SmPC).

The standpoint of the Polish Phytotherapy Association (www.ptfit.org) aims at familiarising doctors with the possible use of herbal medicines in infectious diseases of the respiratory system in children and adults. These medicines may be used in the presence of specific clinical symptoms (local and general, e.g. cough, throat irritation, fever) and/or in case of particular disease entities (e.g. common cold, acute sinusitis, acute bronchitis). This paper is based on the therapeutic-clinical indications and/or disease entity indications of the individual medicines described in the Summary of Product Characteristics (SmPC) according to the International Classification of Diseases-10 (ICD-10), as well as the data contained in EMA/HMPC monographs on herbal substances and current scientific papers, classified in accordance with EBM criteria. Considering the practical nature of the paper, the authors have also decided to provide the proper names of medicinal products used in specific indications.

Herbal medicines and their clinical indications

In the symptomatic treatment of respiratory tract infections, we use medicines of topical and protective action, i.e. antitussive

sive, mucoactive and antimicrobial, as well as those of systemic action, i.e. anti-inflammatory, antipyretic, diaphoretic, immunomodulatory and diuretic. The ingredients of a herbal medicine can be single active substances of plant origin, but they can also be their mixtures (combined medicines). These medicines are administered orally in the form of syrups, oral liquids, capsules or tablets. Medicinal products containing essential oils or their single components (thymol, cineole, menthol, etc.) are administered orally or topically.

Dry cough (nonproductive)

For symptomatic treatment, we use antitussive preparations with a peripheral mechanism of action, which contain plant mucilage. Plant mucilage substances only have a local effect, as they are not absorbed from the mucous membranes and the skin. Plant mucilage is a mixture of polysaccharides characterised by their ability to swell immensely. With water, it forms a colloidal solution (bioadhesive hydrogel), which coats the mucosa with a thin protective layer (mucoadhesion) and provides a protective effect, mechanically reducing the irritation of cough receptors in the epithelium of the upper respiratory tract and the frequency and intensity of the cough reflex, as well as weakening the reflex mechanism, stimulating the emission of bronchial secretions. It also softens the secretion in the upper respiratory tract and thus facilitates its removal. Medicinal products based on mucilaginous herbal substances and/or preparations coat and protect the oral and pharyngeal mucosa against irritable factors, relieve local irritation, redness and inflammation and slightly inhibit the cough reflex [7]. Medicines containing mucilaginous herbal substances can be used safely in children and the elderly, since the biological activity of plant mucilage is weak and, unlike other cough suppressants, does not cause side effects. As plant mucus is not resorbed and is unlikely to reach the trachea and bronchi, therapeutic use in the upper respiratory tract appears to be justified. Traditional herbal medicinal products used to relieve symptoms of irritation of the mucous membrane of the upper respiratory tract (oral cavity and throat) should not be used for more than one week.

Herbal substances (mucinous) used in the treatment of dry cough:

1. **Marshmallow root** (*Althaeae radix*).
2. **Ribwort plantain leaf** (*Plantaginis lanceolatae folium*).
3. **Mullein flower** (*Verbasci flos*).
4. **Iceland moss thallus** (*Lichen islandicus/Cetraria islandica* (L.) *Acharius* s.l., *thallus*).

Marshmallow root (*Althaeae radix*)

Active constituents: The biological activity of the marshmallow root is related to the presence of significant amounts of water-soluble polysaccharides (plant mucilage), pectins and accompanying flavonoids (including glycosides of quercetin and kaempferol), and phenolic acids. In studies on an experimental model in animals, it was shown that both the extract and the isolated polysaccharide markedly reduced the severity and number of coughing episodes; moreover, flavonoids and phenolic acids contributed to the anti-inflammatory effect [8]. **Clinical studies:** Although there is non-clinical data on several actions of the aqueous extract of marshmallow root and/or compounds isolated from it, a direct correlation of these results with clinical practice is not possible. There have been no controlled clinical studies that could support the well-established use of medicinal products made from marshmallow root. The available data is sufficient to support its traditional use. **Indications for use:** Herbal medicinal products containing marshmallow root are traditional medicines with a coating effect, used in the symptomatic treatment of irritation of the mucous membrane of the oral cavity and throat accompanied by a dry cough. They are not recommended in children under 3 years of age. Considering the content of benzoic acid (excipient) in the syrups, caution should

be taken in asthmatic patients. **Detailed information** on selected medicinal products, such as: Syrop prawoślazowy (PPF Hasco-Lek S.A.), Syrop prawoślazowy Althan (PZZ Herbol Poznań S.A.), Syrop prawoślazowy Amara (ZF Amara Sp. z o.o.), Syrop prawoślazowy (Aflofarm Farmacja Polska Sp. z o.o.), ALTE Forte z miodem (PPF Gemi Grzegorz Nowakowski Sp. z o.o.), Alti-Sir (PPH Microfarm Kacperski i wsp. Sp.J.), Syrop prawoślazowy ALTE Forte 6 cz. korzenia prawoślazu (PPF Gemi Grzegorz Nowakowski Sp. z o.o.), Syrop prawoślazowy ALTE (PPF Gemi Grzegorz Nowakowski Sp. z o.o.), Syrop prawoślazowy złożony (upper respiratory tract diseases with nasal mucosa swelling, containing ephedrine hydrochloride, PPF Gemi Grzegorz Nowakowski Sp. z o.o.), Rubital Forte (PPF Gemi Grzegorz Nowakowski Sp. z o.o.), is available in the Summary of Product Characteristics.

Ribwort plantain leaf (*Plantaginis lanceolatae folium*)

Active constituents: The biological activity of ribwort plantain leaf is related to the presence of plant mucilage, iridoid glycosides with aucubin and catalpol as the main compounds, flavonoids (glycosides of apigenin and luteolin), phenylethanoids (verbascoside, among the others), phenolic acids and tannins. Ribwort plantain leaf has local protective actions, as well as exhibits bioadhesive, anti-inflammatory, immunomodulating and epithelial cell stimulating (aucubin) effects. The anti-inflammatory properties of this raw material and its components (aucubin, catalpol, verbascoside, flavonoids) have been documented in *in vitro* and *in vivo* studies. Additionally, some constituents have been attributed spasmolytic (flavonoids, phenylethanoids and iridoids, luteolins, verbascoside and catalpol), antibacterial and antiviral (acteoside, catalpol) properties comparable to atropine and papaverine. Moreover, immunomodulatory effects have been demonstrated for a few compounds of the ribwort plantain leaf, including: polysaccharides, verbascoside, aucubin and catalpol. Combination preparations may have additional properties, e.g. a traditional herbal medicinal product containing a liquid extract of ribwort plantain leaves and a thick extract of echinacea herb, due to the participation of the latter (*Echinaceae purpurea*), which also has properties that stimulate the immune system [9]. **Clinical studies:** There have been no controlled clinical studies that could support the well-established use of medicinal products made from ribwort plantain leaf. The available data is sufficient to support its traditional use. **Indications for use:** Herbal medicinal products with ribwort plantain leaf are traditionally used in the treatment of inflammation of the oral and pharyngeal mucosa, irritation of the oral and pharyngeal mucosa and the associated dry cough. Their use is not recommended in children under 6 years of age (some medicines in Poland are registered for a different age range). **Detailed information** on selected medicinal products, such as: Syrop z babki lancetowatej (PPF Hasco-Lek S.A.), Fiordatussi (Phytopharm Klęka S.A., adults and children 3 years), Lancetan (PF Prolab Sp. z o.o.), Plantagis (PPH Microfarm Kacperski i wsp. Sp.J.), Sirupus Plantaginis PLANTAGEN (PPF Gemi Grzegorz Nowakowski Sp. z o.o.), Plantagopharm (Phytopharm Klęka S.A., adults and children 3 years of age or more), is available in the Summary of Product Characteristics.

Mullein flower (*Verbasci flos*)

Active constituents: The biological activity of mullein flower is related to the content of a mixture of polysaccharides (plant mucilage), iridoid glycosides (aucubin and catalpol), flavonoids (rutin, among others), phenylethanoids (acteoside = verbascoside), as well as triterpene saponins (verbascumsaponins). Mullein flower exhibits local protecting, anti-inflammatory, antimicrobial and antiviral effects (it reduced *in vitro* titres of several strains of influenza A and B viruses, as well as herpes simplex) and has coating and shielding properties. At the same time, saponins determine its expectorant effect. Aucubin, catalpol, acteoside and flavonoids contribute to anti-inflammatory,

spasmolytic and antiviral effects [10]. **Clinical studies:** There have been no controlled clinical studies that could support the well-established use of medicinal products made from mullein flower. The available data is sufficient to support its traditional use. **Indications for use:** Traditionally, mullein flower preparations are used orally to relieve sore throat symptoms associated with a dry cough and the common cold. The use of medicinal products with mullein flower is not recommended in children under 12 years of age. **Detailed information** on selected medicinal products, such as: Syrop z dziewanny (PPF Hasco-Lek S.A.), Noverban (PF Prolab Sp. z o.o.) is available in the Summary of Product Characteristics.

Iceland moss thallus (*Lichen islandicus/Cetraria islandica* (L.) Acharius s.l., thallus)

Active constituents: The biological activity of Iceland moss thallus is attributed to the presence of polysaccharides, mainly lichenin and isolichenin, as well as bitter lichen acids with antimicrobial properties. However, the content of lichen acids, due to their intensely bitter taste, is reduced or minimised in medicinal products with Iceland moss intended for use in respiratory diseases. Iceland moss has a topical protective effect on the mucosa of the upper respiratory tract. In *in vitro* and *in vivo* studies, it has been shown to reduce inflammation and prevent irritation. The bioadhesive effect of isolated Iceland moss polysaccharides has also been confirmed. The aqueous extract increases the activity of phagocytic cells [11]. **Clinical studies:** No controlled clinical studies have yet been conducted to confirm the well-established use of Iceland moss medicinal products. The available data is sufficient to support its traditional use. **Indications for use:** Herbal medicinal products with Iceland moss are used as traditional medicines to alleviate symptoms of irritation of the mucous membrane of the oral cavity and throat accompanied by a dry cough. The use of medicinal products with Iceland moss is not recommended in children under 6 years of age due to lack of relevant data. **Detailed information** on the medicinal product, such as: Herbion na kaszel (Krka, d.d., Nove mesto) is available in the Summary of Product Characteristics.

Wet cough (productive)

Herbal medicines used to cleanse the respiratory tract of retained secretions have secretolytic action (they liquefy bronchial secretions), as well as secretomotor (they stimulate cilia movement and mucus transport) and expectorant (they facilitate the excretion of bronchial secretions) effects [4, 5]. Herbal expectorants are divided into several groups depending on their mechanism of action, but most of them have a mixed mode of action [7]. The herbal active substances contained in the medicines used in a productive (wet) cough show complex mechanisms of action. Apart from their properties that facilitate the removal of secretions obstructing the respiratory tract, they also exhibit anti-inflammatory, antioxidant, antiseptic, antiviral, antibacterial, antifungal and other properties presented in detail for individual herbal medicinal products. Herbal substances containing saponins and their preparations administered orally irritate nerve endings in the gastric mucosa, causing reflexively increased secretion of larger amounts of liquid mucus by the bronchi [7]. Essential oil-containing herbal substances and isolated from them essential oils, as well as their single chemical constituents (thymol, cineol etc), in oral and inhaled administration, directly irritate the bronchial glands and mucosa of the respiratory tract, stimulating the secretion of more fluid mucus. The constituents of essential oils are well absorbed in the gastrointestinal tract (unlike saponins) and partially excreted through the respiratory tract. In the case of herbal medicines containing saponins and essential oils, caution should be taken in patients with gastritis or peptic ulcer disease. Doses that are too high can cause nausea, vomiting, diarrhoea or exacerbate pain.

Plant substances used in treatment of wet (productive) cough:

1. **Ivy leaf (*Hederae folium*).**
2. **Thyme herb (*Thymi herba*), thyme essential oil of the thymol type (*Thymi typo thymolo aetheroleum*), thymol (*Thymolum*).**
3. **Primula root (*Primulae radix*).**
4. **Eucalyptus leaf (*Eucalypti folium*), eucalyptus essential oil (*Eucalypti aetheroleum*), cineole** (detailed description can be found in StanPhyto RESPIRATORY II).
5. **Young pine shoots (sprouts) (*Pini turiones*), spring pine buds (*Pini gemmae*), pine essential oil (*Pini sylvestris aetheroleum*).**
6. **Fennel fruit (*Foeniculi fructus*).**
7. **Herbal active substances in a multi-component medicinal product: Thyme herb (*Thymus vulgaris* L. or *Thymus zygis* L., *herba*), Iceland moss thallus (*Cetraria islandica* (L.) Acharius s.l., *thallus*), hyssop herb (*Hyssopus officinalis* L., *herba*), soapwort root (*Saponaria officinalis* L., *radix*).**

Ivy leaf (*Hederae folium*)

Active constituents: Among the biologically active constituents of ivy leaf, triterpene saponins predominate, of which hederacoside C is metabolised to α -hederine, which has bronchodilating effects (β_2 -adrenergic receptors) and secretolytic properties [12]. Studies have shown that α -hederin, but not hederacoside C and hederagenin, regulates β_2 -adrenergic receptor activity by stimulating surfactant production in type II alveolar pneumocytes [13]. In animal model studies, the anti-inflammatory effect of dry ivy leaf extract was demonstrated by inhibition of the LPS-induced release of IL-6 from murine macrophages [14]. A reduced inflammatory cell response of various human cell lines, including, for the first time, lung epithelial cells (A549), was also observed. *Hedera helix*, ivy leaf preparation (EA 575[®]), was shown to regulate the NF κ B pathway, possibly by changing the specificity of IKK from I κ B α to RelA, resulting in increased stability of the NF κ B:I κ B α complex and decreased translocation of RelA to the nucleus. The effective reduction of NF κ B translocation to the cell nucleus appears to be the main mechanism for the anti-inflammatory effect of EA 575[®] [15]. **Clinical studies:** The efficacy of treatment with dry ivy leaf extract (DER 5–7,5: 1) has been confirmed in adults in placebo-randomised controlled clinical trials [DER 5–7.5: 1 (Drug Extract Ratio) means that from 5–7.5 g of raw material 1 g of extract was obtained] [16, 17]. Controlled studies also confirmed the effectiveness of dry ivy leaf extracts in preparations with quality parameters DER 4–8: 1 and DER 3–6: 1, and the analysis of these studies was systematically reviewed [18]. In children, a major clinical improvement in the 7-day therapy of acute bronchitis was observed in a non-interventional study involving over 1,000 school-aged children (6–12 years) [19]. A study by Kruttschnitt et al. indicated that children and adults treated with ivy leaf extract or acetylcysteine showed a comparable improvement in respiratory functions [20]. Efficacy and safety study of bronchitis treatment with ivy leaf extract (DER 2.2–2.9:1) in 267 children in two independent, open-label, non-interventional studies showed clinical improvement and good treatment tolerance [21]. In a double-blind, placebo-controlled, randomised, *cross-over* study, 30 children with partially controlled or uncontrolled asthma, treated with 400 μ g budesonide equivalent, were additionally given dry ivy leaf extract vs. placebo for four weeks. Significant improvements in MEF (75–25), MEF25 and VC were found, which indicates that the inclusion of a dry extract of common ivy leaf may be beneficial in the treatment of asthma. However, further studies are needed in this area [22]. The efficacy and safety of the dry extract of common ivy leaf in the treatment of acute inflammatory conditions of the respiratory tract, accompanied by a productive cough, including acute bronchitis of various aetiologies or

exacerbations of chronic bronchitis, have also been confirmed by other clinical studies [23]. Based on controlled clinical trials, ivy leaf medicinal products are classified as well-established medicinal products. These include dry extracts (DER 4–8: 1), (DER 6–7: 1), (DER 3–6: 1) and liquid extracts (DER 1: 1) and soft extracts (DER 2.2–2.9: 1) [24]. **Other recommendations:** The efficacy of treatment with standardised ivy leaf preparations for acute bronchitis in adults is confirmed by national recommendations for the management of respiratory infections [25]. **Indications for use:** Herbal medicinal products with dry extract of ivy leaf are used as an expectorant for productive (wet) cough. They are not recommended in children under 2 years of age. **Detailed information** on selected medicinal products, such as: Hederasal (Wrocławskie Zakłady Zielarskie Herbapol S.A.), Hederasal Max (Wrocławskie Zakłady Zielarskie Herbapol S.A., adults and children 12 years of age or more), Hedussin (Phytopharm Kłęka S.A.), Hadelix (Krewel Meuselbach GmbH), Herbion na kaszel mokry (Krka, d.d., Nove mesto), Hedripsam (Dr MAX Pharma), Hedecton (Krewel Meuselbach GmbH), Helituspan (Sopharma AD), Hederoin (Wrocławskie Zakłady Zielarskie Herbapol S.A., adults and children 6 years of age or more), Hadelix (Fortis Pharmaceuticals Sp. z o.o.), Mucoplant na kaszel bluszcz (Dr. Theiss Naturwaren GmbH), Mucoplant na kaszel bluszcz forte (Dr. Theiss Naturwaren GmbH), Pectolvan (Farmak International Sp. z o.o.), Pini Helix (Farmina Sp. z o.o., adults and children 12 years of age or more with indication for common cold), Prospan (Engelhard Arzneimittel GmbH & Co.KG), Prospan pastylki miękkie (Engelhard Arzneimittel GmbH & Co.KG), is available in the Summary of Product Characteristics.

Thyme herb (*Thymi herba*)

Active constituents: The main biologically active constituent of thyme herb is the essential oil containing thymol and carvacrol, compounds with strong antimicrobial properties. Moreover, flavonoid compounds, phenolic acids (caffeic acid esters previously referred to as *Labiatae-type* tannins), including rosmarinic acid, are present. The active constituents of thyme herb have antibacterial, expectorant and diastolic effects and influence the motility and function of the respiratory epithelium, thus accelerating the evacuation of residual mucus [26–28]. Rosmarinic acid exhibits strong antioxidant and antimicrobial properties. Thyme extracts exert an anti-inflammatory action by inhibiting hyaluronidase activity, reducing the secretion of prostaglandins and pro-inflammatory cytokines and increasing the IL-10 level [29]. An antiviral activity has also been shown through the effects on the main external proteins of the influenza virus: haemagglutinin and neuraminidase [30]. **Clinical studies:** In a randomised double-blind study in patients with acute bronchitis treated with thyme herb and primrose root, a combination herbal medicine, a significant reduction in symptoms and a major reduction in the duration of illness were observed [31]. Another placebo-controlled study observed 361 patients with acute bronchitis. Reduction in cough was 67.1% in the study group compared to 51.3% in the placebo group. In addition, up to 50% cough relief was observed two days earlier in the group of patients taking the medicine than in the control group, and the bronchitis symptoms also disappeared faster [32]. Observational studies have shown effectiveness at least comparable to preparations containing ambroxol (so-called non-inferiority), with more effective relief of cough and dyspnoea. Patients also consider it a safer drug [33]. The controlled clinical studies conducted to date have not yet allowed for confirmation of the established use of medicinal products with thyme. The available data is sufficient to support its traditional use [34]. **Indications for use:** Herbal medicinal products with thyme herb are used traditionally as an expectorant for wet cough, and difficulties in expectoration during respiratory tract infections. The use of the herbal medicinal products in children under 6 years of age is not recommended due to insufficient data. **Detailed information** on selected herbal medicinal products, such as: Bronchicum T

(Opella Healthcare Poland Sp. z o.o.), Bronchosol (Phytopharm Kłęka S.A., combination medicine, adults and children 4 years of age or more), Bronchosol Solid (Phytopharm Kłęka S.A., combination medication, adults and children 12 years of age or more), Bronchostop na kaszel (Kwizda Pharma GmbH), Bronchostop na kaszel Duo (Kwizda Pharma GmbH, adults and children 3 years of age or more), Sallevia (Conforma NV), Syrop tymiankowy złożony (PPF Hasco-Lek S.A.), Syrop tymiankowy złożony (ZF Amara SP), Syrop tymiankowy złożony (Wrocławskie Zakłady Zielarskie Herbapol S.A., adults and children 12 years of age or more), Syrop tymiankowy złożony Gemi (PPF Gemi Grzegorz Nowakowski), Syrop tymiankowy złożony (Herbapol Lublin S.A.), Syrop tymiankowy złożony Aflofarm (Aflofarm Farmacja Polska Sp. z o.o.), is available in the Summary of Product Characteristics.

Primula root (*Primulae radix*)

Active constituents: Biological activity is demonstrated by saponin (triterpene) compounds, oleanolic acid derivatives (including primulasaponin A – primulic acid, in addition to the phenolic glycosides primulaveroside and primveroside, i.e. salicylic acid derivatives. *In vitro* studies have demonstrated the antibacterial, antifungal and antiviral activities of saponins of primrose root. The extracts inhibited the release of IL-8 induced by COX-1, COX-2 and LPS in human monocytes. *In vivo* studies in animals revealed an increase in epithelial cilia activity and pain inhibition in an inflammatory model in a dose-dependent manner with primrose root saponins [35]. Saponins reflexively, by irritating the gastric mucosa, increase the secretion of mucus in the respiratory tract, liquefy retained secretions and enhance the expectorant reflex by having a positive effect on the epithelium and stimulating the functioning of cilia. **Clinical studies:** There have been no controlled clinical studies to date to support the well-established use of medicinal products with primrose root. Sufficient data is available to support its traditional use [36]. There are no single-ingredient herbal medicines of primrose root registered in Poland, only combination herbal products containing extracts of thyme herb, coltsfoot leaf and other compositions. **Indications for use:** Indications for their use as a traditional medicinal product include, depending on the composition: dry cough and difficult expectoration, wet cough with excess secretion. Primrose root extract is contraindicated in gastritis and gastric ulcer disease, in children with a history of acute laryngitis and tracheitis and in the case of asthma. **Detailed information** on selected medicinal products, such as: Bronchitabs (Bionorica SE, adults 18 years of age or more), Herbapect (Aflofarm Farmacja Polska, adults and children 4 years of age or more) is available in the Summary of Product Characteristics.

Eucalyptus leaf (*Eucalypti folium*), eucalyptus essential oil (*Eucalypti aetheroleum*), cineole (detailed description can be found in StanPhyto RESPIRATORY II).

Young pine shoots (sprouts) (*Pini turiones*), spring pine buds (*Pini gemmae*), pine essential oil (*Pini sylvestris aetheroleum*)

Active constituents: They contain essential oil (approx. 0.4%), the composition of which includes, among the others, α -pinene and β -pinene, Δ 3-carene, camphene, borneol, limonene and others, as well as diterpenic acids, juniperic and sabinic acid derivatives, resins, bitter compounds and tannins. Pine oil (*Pini sylvestris oleum*) has an expectorant (secretolytic) action, as it increases ciliary movement in the respiratory epithelium, as well as bactericidal and diastolic effects [37]. The antimicrobial activity of the oil and its constituents has been demonstrated against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Candida albicans* [38]. **Clinical studies:** There have been no controlled clinical studies to date to support the well-established use of medicinal products. **Indications for use:** Medicinal products indicated for use as an expectorant, as adjunctive treatment in upper respiratory tract

inflammation. **Additional indications:** Pine shoot preparations are also found in combination products, and the indication for their use is a dry strenuous cough in the course of upper respiratory tract infections. *Sirupus pini compositus* contains pine shoot preparation, fennel tincture and codeine phosphate, an opioid substance with a central antitussive effect. Dexapini syrup contains pine shoot preparation, fennel tincture and dextromethorphan, an opioid substance with a central antitussive effect. **Detailed information** on selected herbal medicinal products, such as: Syrop z sosny i kopru włoskiego (PPF Hasco-Lek S.A., combination medicine, adults and children 6 years of age or more), Sirupus Pini compositus (Wrocławskie Zakłady Zielarskie Herbapol S.A., combination medicine, adults and children 12 years of age or more), Dexapini (Zakłady Farmaceutyczne POLPHARMA S.A., adults and children 6 years of age or more), is available in the Summary of Product Characteristics.

Fennel fruit (*Foeniculi fructus*)

Active constituents: The main biologically active constituent of fennel fruit is an essential oil containing anethole (80–60%), fenchone (25–6%) and estragole (4–6%), in variable concentrations depending on the fennel variety (bitter fennel or sweet fennel). Other constituents include α -pinene, limonene, camphene, β -pinene, anethole, β -myrcene, *p*-cymene and anisaldehyde. Other constituents of both bitter and sweet fennel fruits are water-soluble glycosides of the same monoterpenoids that are present as free forms in the oil, as well as other phenolic compounds [39]. Extensive studies have been conducted on fennel and its essential oil. Previous *in vivo* pharmacological studies demonstrated gastrointestinal, as well as respiratory tract diastolic effects, such as bronchodilatation and relaxation of the tracheal smooth muscles. Secretolytic and expectorant (*expectorantia*) effects through a reflex action by irritation of the gastric mucosa and induction of a secretolytic effect in the bronchi have also been shown. Antimicrobial – antiviral, antibacterial, antifungal activity of the essential oil constituents have also been described as a result of disruption of the integrity of the cell membranes of bacteria and fungi, which leads to coagulation of the cytoplasm and lysis of their cells [40]. **Clinical studies:** No controlled clinical studies have yet been conducted to support the well-established use of fennel medicinal products. Sufficient data is available to support its traditional use. **Indications for use:** Herbal medicinal products indicated for use as an expectorant, as adjunctive treatment in inflammation of the upper respiratory tract. **Additional indications:** fennel fruit preparations are also present in combination herbal products, and the indication for their use is dry strenuous cough in the course of upper respiratory tract infections. *Sirupus Pini compositus* contains preparation of pine shoots, fennel tincture and codeine phosphate – an opioid substance with a central antitussive effect; Dexapini contains preparation of pine shoots, fennel tincture and dextromethorphan – non-opioid substance with a central antitussive effects. **Detailed information** on selected herbal medicinal products, such as: Syrop z sosny i kopru włoskiego (PPF Hasco-Lek S.A., combination medicine, adults and children 6 years of age or more), Sirupus Pini compositus (Wrocławskie Zakłady Zielarskie Herbapol S.A., combination medication, adults and youth 12 of age years or more), Dexapini (Zakłady Farmaceutyczne POLPHARMA S.A., adults and children 6 years of age or more), is available in the Summary of Product Characteristics.

Herbal substances in a multi-component medicinal product: thyme herb (*Thymus vulgaris* L. or *Thymus zygis* L., *herba*), Iceland moss (*Cetraria islandica* (L.) *Acharius* s.l., *thallus*), hyssop herb (*Hyssopus officinalis* L., *herba*), soapwort root (*Saponaria officinalis* L., *radix*)

Active constituents: The biological effects and chemical composition of *Thymi herba* (*Thymus vulgaris* L. or *Thymus zygis* L., *herba*) and Iceland moss thallus (*Cetraria islandica* (L.) *Acharius* s.l., *thallus*) are presented in the characteristics of individual

herbal substances. Soapwort root contains oleanane-derived saponin compounds, which include, among others, gypsogenic, hydroxygypsogenic and quillaic acid derivatives and gypsogenin derivatives (approximately 2–8%). Saponins determine the expectorant effect of soapwort root, based on the mechanism of action typical of this group of secondary metabolites. Antifungal activity against *Candida albicans* has been revealed for the soapwort root extract. The antimicrobial properties of soapwort root are associated with the presence of saponins, while those of hyssop herb are linked to the presence of essential oils (main constituents of isopinocampone (40–50%) pinocampone (10%), β -pinene, terpinen-4-ol, pinocarvone, carvacrol, *p*-cymene and myrtenal) [41, 42]. The strong antimicrobial activity of this essential oil has been shown against *Staphylococcus pyogenes*, *Staphylococcus aureus*, *Candida albicans* and *Escherichia coli*, but not against *Pseudomonas aeruginosa* [43]. The combination of the above-presented herbal substances has an expectorant effect (thyme herb, hyssop herb, soapwort root) and protective function for the mucous membrane of the upper respiratory tract (antitussive) (Iceland moss thallus) as a result of the activity of the biologically active compounds (saponins, essential oils, mucilage) and their synergistic interactions. Moreover, the action profiles of all the herbal active substances mentioned above highlight their antimicrobial effects, including Iceland moss thallus. Due to the content of lichen acids, this plant raw material inhibits the growth of pathogenic microorganisms (some Gram (+) bacteria) and stimulates the secretion from digestive glands (bitter protolychesteric and fumaroprotocetraric acids stimulate appetite and digestion). Due to the presence of thyme herb and hyssop, containing polyphenolic compounds (phenolic acids, flavonoids) and triterpenes, the medication will also exhibit antioxidant and anti-inflammatory properties [44, 45]. **Clinical studies:** There have been no controlled clinical studies to date to support the well-established use of a combined medicinal products. The available data is sufficient to support its traditional use. **Indications for use:** Traditional herbal medicinal product for inflammation of the upper respiratory tract and difficult expectoration with excess secretion, adults and children 12 years of age or more. **Detailed information** on the medicinal product Pectosol (ZF POLPHARMA S.A.) is available in the Summary of Product Characteristics.

Herbal medicines with clinical indications for the treatment of fever

Fever

Fever, being one of the primary defence mechanisms in response to an infectious agent, is a frequent and common general symptom in infections of the respiratory tract. Normal body temperature varies, among others, with age, time of day, activity level and phase of the menstrual cycle. Generally, infants and young children have a higher temperature than older children and adults. This is related to the higher body surface area to body weight ratio and faster metabolism in infants and young children. In the neonatal period, the average normal temperature (measured via the rectum) is 37.5°C, with an upper limit of normal of 38°C. In adults, the mean body temperature ranges between 36.1–37.5°C. In older people, the temperature is slightly lower and does not exceed 37°C. Clinically, a fever is a body temperature of at least 1°C above the mean normal/normal temperature at the site of measurement [46]. The herbal medicines that we use in patients may contain single herbal active substances (preparations). Combination medicines with a wider range of biological activity that are beneficial in the treatment of respiratory infections are also available. Herbal substances used in medicines for sub-febrile conditions include:

Herbal substances used in the treatment of fever (subfebrile conditions):

1. Willow bark (*Salicis cortex*)

Willow bark (*Salicis cortex*)

Active constituents: Willow bark contains salicylic alcohol derivatives, including its glycoside – salicin and salicin ester – salicortin and many others, next to, flavonoid compounds of the chalcone and flavanone group, as well as flavan-3-ol derivatives: monomeric (catechin) and dimeric (proanthocyanidins), and phenolic acids are also present. Anti-inflammatory, antioxidant effects were observed due to the presence of a rich complex of polyphenols and salicylic compounds. *In vivo* and *in vitro* studies have shown that willow bark extract inhibits cyclooxygenase-2 and lipoxygenase, pro-inflammatory cytokine release and NFκ-B activation and also inhibits swelling in an inflammation model

induced by carrageenan administration. In *in vivo* studies, an antipyretic effect was demonstrated for salicin in a model of fever induced by carrageenan, carrageenin LPS and yeast. The potency of the antipyretic effect for this plant raw material and the related preparations has not been defined in studies [47, 48]. **Clinical studies:** There have been no controlled clinical studies to date to support the well-established use of medicinal products with willow bark in the treatment of fever. The available data is sufficient to support its traditional use [48]. **Indications for use:** Willow bark herbal medicinal products are traditional herbal medicines used in adults 18 years of age or more in sub-febrile conditions (fever) accompanying a common cold. **Detailed information** on selected medicinal products, such as: Salicortex (Laboratorium Farmaceutyczne Labofarm Sp. z o.o. Sp. K.) is available in the Summary of Product Characteristics.

Source of funding: This work was funded from the authors' own resources.

Description of a potential conflict of interest. Zbigniew Doniec – lectures for pharmaceutical companies: Wrocławskie Zakłady Zielarskie Herbapol S.A., PPF Hasco-Lek S.A., Phytopharm Kleka S.A., US Pharmacia Sp. z o.o., Bionorica Polska Sp. z o.o.; Ernest Kuchar – lectures for pharmaceutical companies: Wrocławskie Zakłady Zielarskie Herbapol S.A., PPF Hasco-Lek S.A., Bionorica Polska Sp. z o.o., Salveo Poland Sp. z o.o.; Mirosława Krauze-Baranowska – lectures for pharmaceutical companies: Wrocławskie Zakłady Zielarskie Herbapol S.A., Bionorica Polska Sp. z o.o. The other authors do not declare a conflict of interest.

References

- Denny FW Jr. The clinical impact of human respiratory virus infections. *Am J Respir Crit Care Med* 1995; 152(4 Pt 2): S4–S12, doi: 10.1164/ajrcm/152.4_Pt_2.S4.
- Berman S. Otitis Media in Developing Countries. *Pediatrics* 1995; 96(1 Pt 1): 126–131.
- Undrunas A, Kuziemski K. Uporczywy kaszel – trudności diagnostyczno-terapeutyczne w codziennej praktyce lekarskiej. *Forum Med Rodz* 2017; 11(4): 149–155 (in Polish).
- Krenke K, Doniec Z, Mastalerz-Migas M, et al. Zalecenia postępowania diagnostyczno-terapeutycznego w kaszlu u dzieci – aktualizacja. *Lekarz POZ* 2022; 3: 173–192 (in Polish).
- Schönknecht K, Krauss H, Jambor J, et al. Treatment of cough in respiratory tract infections – the effect of combining the natural active compounds with thymol. *Wiad Lek* 2016; 69(6): 791–798.
- Committee on Herbal Medicinal Products (HMPC). Available from URL: <https://www.ema.europa.eu/en/committees/committee-herbal-medicinal-products-hmpc>.
- Farmakopea Polska wydanie XII. Available from URL: <https://urpl.gov.pl/pl/urz%C4%85d/farmakopea/farmakopea-polska> (in Polish).
- European Union herbal monograph on *Althaea officinalis* L., radix; EMA/HMPC/436679/2015. Available from URL: https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-althaea-officialis-l-radix_en.pdf.
- Assessment report on *Plantago lanceolata* L., folium; EMA/HMPC/437859/2010. Community herbal monograph on *Plantago lanceolata* L., folium; EMA/HMPC/437858/2010 Corr. Available from URL: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-plantago-lanceolata-l-folium_en.pdf.
- Assessment report on *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad) and *V. phlomoides* L., flos; EMA/HMPC/611531/2016, European Union herbal monograph on *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad) and *V. phlomoides* L., flos; EMA/HMPC/611537/2016. Available from URL: https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-verbascum-thapsus-l-v-densiflorum-bertol-v-thapsiforme-schrad_en.pdf.
- Assessment report on *Cetraria islandica* (L.) Acharius s.l., thallus; EMA/HMPC/36866/2014 European Union herbal monograph on *Cetraria islandica* (L.) Acharius s.l., thallus; EMA/HMPC/678891/2013. Available from URL: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-cetraria-islandica-l-acharius-sl-thallus-first-version_en.pdf.
- Assessment report on *Hedera helix* L., folium. 28 January 2015; EMA/HMPC/586887/2014 Committee on Herbal Medicinal Products (HMPC). Available from URL: https://www.ema.europa.eu/en/documents/herbal-report/draft-assessment-report-hedera-helix-l-folium_en.pdf.
- Sieben A, Prenner L, Sorkalla T, et al. Alpha-hederin, but not hederacoside C and hederagenin from *Hedera helix*, affects the winding behavior, dynamics and regulation of beta2-adrenergic receptors. *Biochemistry* 2009; 48: 3477–3482.
- Schulte-Michels J, Runkel F, Gokorsch S, et al. Ivy leaves dry extract EA 575® decreases LPS-induced IL-6 release from murine macrophages. *Pharmazie* 2016; 71(3): 158–161.
- Schulte-Michels J, Kexsel C, Häberlein H, et al. Anti-inflammatory effects of ivy leaves dry extract: influence on transcriptional activity of NFκB. *Inflammopharmacology* 2019; 27(2): 339–347, doi: 10.1007/s10787-018-0494-9.
- Schaefer A, Ludwig F, Giannetti BM, et al. Efficacy of two dosing schemes of a liquid containing ivy leaves dry extract EA 575® versus placebo in the treatment of acute bronchitis in adults. *ERJ Open Res* 2019; 5: 00019–2019.
- Schaefer A, Kehr MS, Giannetti BM et al. A randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of a liquid containing ivy leaves dry extract (EA 575®) vs. placebo in the treatment of adults with acute cough. *Pharmazie* 2016; 71: 504–509.
- Holzinger F, Chenot JF. Systematic review of clinical trials assessing the effectiveness of ivy leaf (*Hedera helix*) for acute upper respiratory tract infections. *Evid Based Complement Alternat Med* 2011; 2011: 382789.
- Lang C, Staiger C, Wegener T. Ivy in everyday paediatric use: administration of EA 5751 to schoolchildren for the treatment of acute bronchitis. *Z Phytother* 2015; 36: 192–196.
- Kruttschnitt E, Wegener T, Zahner C, et al. Assessment of the efficacy and safety of ivy leaf (*Hedera helix*) cough syrup compared with acetylcysteine in adults and children with acute bronchitis. *Evid Based Complement Alternat Med* 2020; 2020: 1910656.
- Schmidt M, Thomsen M, Schmidt U. Suitability of ivy extract for the treatment of paediatric cough. *Phytother Res* 2012; 26(12): 1942–1947, doi: 10.1002/ptr.4671.
- Zeil S, Schwanebeck U, Vogelberg C. Tolerance and effect of an add-on treatment with a cough medicine containing ivy leaves dry extract on lung function in children with bronchial asthma. *Phytomedicine* 2014; 21(10): 1216–1220, doi: 10.1016/j.phymed.2014.05.006.

23. Lang C, Röttger-Lüer P, Staiger C. A valuable option for the treatment of respiratory diseases: review on the clinical evidence of the ivy leaves dry extract EA 575®. *Planta Med* 2015; 81: 968–974.
24. European Union herbal monograph on *Hedera helix* L., folium, 21 November 2017 EMA/HMPC/325716/2017 Committee on Herbal Medicinal Products (HMPC). Available from URL: https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-hedera-helix-l-folium-revision-2_en.pdf.
25. Hryniewicz W, Albecht P, Radzikowski A, eds. Rekomendacje postępowania w pozaszpitalnych zakażeniach układu oddechowego. Dostępny na URL: <https://antybiotyki.edu.pl/wp-content/uploads/Rekomendacje/Rekomendacje2016.pdf> (in Polish).
26. Wienkotter N, Begrow F, Kinzinger U, et al. The effect of thyme extract on beta2-receptors and mucociliary clearance. *Planta Med* 2007; 73: 629–635.
27. Hammad M, Sallal AK, Darmani H. Inhibition of *Streptococcus mutans* adhesion to buccal epithelial cells by an aqueous extract of *Thymus vulgaris*. *Int J Dent Hygiene* 2007; 5: 232–233.
28. Tohidpour A, Sattari M, Omidbaigi R, et al. Antibacterial effect of essential oils from two medicinal plants against Methicillin-resistant *Staphylococcus aureus* (MRSA). *Phytomed* 2010; 17: 142–145.
29. Ocaña A, Reglero G. Effects of thyme extract oils (from *Thymus vulgaris*, *Thymus zygis*, and *Thymus hyemalis*) on cytokine production and gene expression of oxLDL-stimulated THP-1-macrophages. *J Obes* 2012; 2012: 10470.
30. Vimalanathan S, Hudson J. Anti-influenza virus activity of essential oils and vapors. *Amer J Essential Oils Nat Prod* 2014; 2: 47–53.
31. Gruenwald J, Graubaum HJ, Busch R. Efficacy and tolerability of a fixed combination of thyme and primrose root in patients with acute bronchitis. A double-blind, randomized, placebo controlled clinical trial. *Arzneimittelforschung* 2005; 55: 669–676.
32. Kemmerich B. Evaluation of efficacy and tolerability of a fixed combination of dry extracts of thyme herb and primrose root in adults suffering from acute bronchitis with productive cough. A prospective, double-blind, placebocontrolled multicentre clinical trial. *Arzneimittelforschung* 2007; 57: 607–615.
33. Fal AM, Schönknecht K. Skuteczność i tolerancja syropu Bronchosol® w leczeniu ostrego zapalenia oskrzeli u dorosłych. Porównanie z preparatami syntetycznymi zawierającymi ambroksol – badanie obserwacyjne. *Wiad Lek* 2015; LXVIII(2): 139–144 (in Polish).
34. Assessment report on *Thymus vulgaris* L., *vulgaris zygis* L., herba. 12 November 2013 EMA/HMPC/342334/2013 Committee on Herbal Medicinal Products (HMPC). Available from URL: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-thymus-vulgaris-l-vulgaris-zygis-l-herba_en.pdf.
35. *Primulae radix* (Primula root). Available from URL: <https://escop.com/downloads/primulae-radix-primula-root-escop-2021/>.
36. Community herbal monograph on *Primula veris* L. and/or *Primula elatior* (L.) Hill, radix, 19 September 2012 EMA/HMPC/104095/2012 Committee on Herbal Medicinal Products (HMPC). Available from URL: https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-primula-veris-l-primula-elatior-l-hill-radix_en.pdf.
37. Nurzyńska-Wierdak R. Aktywność biologiczna olejów eterycznych roślin z rodziny Pinaceae. *Ann UMCS Sectio EEE Horticultura* 2015; XXV(3): 19–31 (in Polish).
38. Rivas da Silva AC, Monteiro Lopes P, Barros de Azevedo MM, et al. Biological activities of α -pinene and β -pinene enantiomers. *Molecules* 2012; 17: 6305–6316.
39. ESCOP Monographs. *Foeniculi fructus*. Available from URL: <https://escop.com/wp-content/uploads/edd/2019/03/Foeniculi-fructus-ESCOP-2019.pdf>.
40. Zalewska E, Nurzyńska-Wierdak R. Rośliny z rodziny Apiaceae źródłem surowca farmakopealnego. *Ann UMCS Sectio EEE Horticultura* 2016; XXVI(2): 47–60 (in Polish).
41. Chandra S, Rawat DS, Bhatt A. Phytochemistry and pharmacological activities of *Saponaria officinalis* L.: A review. *Notulae Scientia Biologicae* 2021; 13(1): 10809.
42. Jop B, Krajewska A, Wawrzyńczak K, et al. Phytotoxic Effect of Essential Oil from Hyssop (*Hyssopus officinalis* L.) against Spring Wheat and White Mustard. *Biol Life Sci Forum* 2021; 3(1): 13, doi: 10.3390/IECAG2021-09711.
43. Kizil S, Hasimi N, Tolan V, et al. Chemical Composition, Antimicrobial and Antioxidant Activities of Hyssop (*Hyssopus officinalis* L.) Essential Oil. *Not Bot Hort Agrobot Cluj* 2010; 38(3): 99–103.
44. Devi KP, Malar DS, Nabavi SF, et al. Kaempferol and inflammation: From chemistry to medicine. *Pharmacol Res* 2015; 99: 1–10, doi: 10.1016/j.phrs.2015.05.002.
45. Schulz V, Hansel R, Tyler VE. *Rational phytotherapy. A physicians guide to herbal medicine*. Berlin: Springer; 2001.
46. Sybilski AJ. *Gorączka*. In: Sybilski AJ, Woron J, Życińska K, et al., eds. *Gorączka, przyczyny, diagnostyka, leczenie*. Warszawa: Medical Education; 2021: 53–65 (in Polish).
47. European Union herbal monograph on *Salix* [various species including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], cortex. Available from URL: https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-salix-various-species-including-s-purpurea-l-s-daphnoides-vill_en.pdf.
48. Edwards SE, Costa Rocha I, de, Williamson EM, et al. *Fitofarmaceutyki – oparte na dowodach naukowych kompendium leczniczych produktów ziołowych*. Warszawa: Wydawnictwo Lekarskie PZWL; 2022 (in Polish).

Tables: 0

Figures: 0

References: 48

Received: 21.08.2023

Reviewed: 04.09.2023

Accepted: 16.09.2023

Address for correspondence:

Zbigniew Doniec, Md, PhD, Assoc. Prof.

Klinika Pneumonologii, Instytut Gruźlicy i Chorób Płuc OT w Rabce-Zdroju

ul. Prof. J. Rudnika 3B

34-700 Rabka Zdrój

Polska

Tel.: +48 18 2676060

E-mail: zdoniec@igrabka.edu.pl