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REVIEW ARTICLE

New treatment options for acute rhinosinusitis according to EPOS 2020

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ABSTRACT: Acute rhinosinusitis (ARS) is a very common condition and mostly of viral origin. About 0.5–2% of cases of viral ARS are complicated by a bacterial infection. Due to viral etiology and inflammatory mechanisms of rhinitis and rhinosinusitis, symptomatic treatment including phytotherapy has been used for their treatment for decades. Scientific societies and expert groups recommend the use of herbal medicines in acute viral and acute postviral rhinosinusitis. In 2021, Polish patients gained access to a new therapeutic option for acute sinusitis in the form of a drug containing a distillate of a mixture of rectified essential oils of eucalyptus, sweet orange, myrtle and lemon common.

KEYWORDS: essential oils, eucalyptus, myrtle and lemon common, phytotherapy, rhinosinusitis accute, sweet orange

ABBREVIATIONS

ABRS – acute bacterial rhinosinusitis
ARPS – acute rhinitis and paranasal sinusitis
CRP – C-reactive protein
EPOS – Position Paper on Rhinosinusitis and Nasal Polyps
ESR – erythrocyte sedimentation rate
Gtf – glucosyl transferase

INTRODUCTION

Acute rhinosinusitis (ARS) is a very common condition and mostly of viral origin [1, 2]. Bacterial infection is observed in only about 0.5–2% of cases of viral ARS [1, 2]. At the moment, we still do not have causal, antiviral treatment allowing for e*ffective prevention and treatment of ARS. Recommendations for* the treatment of out-of-hospital respiratory infections [2], containing recommendations for pharmacotherapy of acute sinusitis, issued by the National Institute of Health, recommend the use of symptomatic agents in viral ARS, i.e.: analgesics and antipyretics, nasal rinses with saline solution, nasal decongestants, nasal preparations with ipratroprium bromide as well as plant-based drugs with a secretolytic action.

Further in this paper, we present the definition of rhinosinusitis according to EPOS 2020 (European Position Paper on Rhinosinusitis and Nasal Polyps) [1].

Rhinosinusitis in adults is characterized by (clinical definition) [1]:

- two or more symptoms, one of which should be:
  - nasal blockage/swelling/impaired nasal patency, *or*
  - nasal discharge (anterior/posterior nasal drip)

and

+/- pain/sensation of increased pressure in the face,
+/- loss of smell

and/or

- findings in endoscopic examination:
  - nasal polyps *and/or*
  - mucopurulent secretions, mainly in the middle nasal meatus

and/or

- swelling of the mucous membrane, mainly in the middle nasal passage,

and/or

- findings in computed tomography:
  - changes to the mucous membrane within the ostiomeatal complex and/or sinuses.

The definition of sinusitis in children is like the one presented above. The only difference is that the symptom of loss of smell has been replaced by another, i.e., cough.

In everyday medical practice, as well as in epidemiological studies, the definition of rhinosinusitis is based on symptomatology, usually without ENT examination or radiological diagnosis [1]. Thus, the diagnosis can be made based on history taken during a personal visit or telephone conversation [1, 3].

Due to duration of clinical manifestations, rhinosinusitis is distinguished into [1]:

- acute rhinosinusitis – symptoms lasting less than 12 weeks,
- chronic rhinosinusitis – symptoms lasting more than 12 weeks.

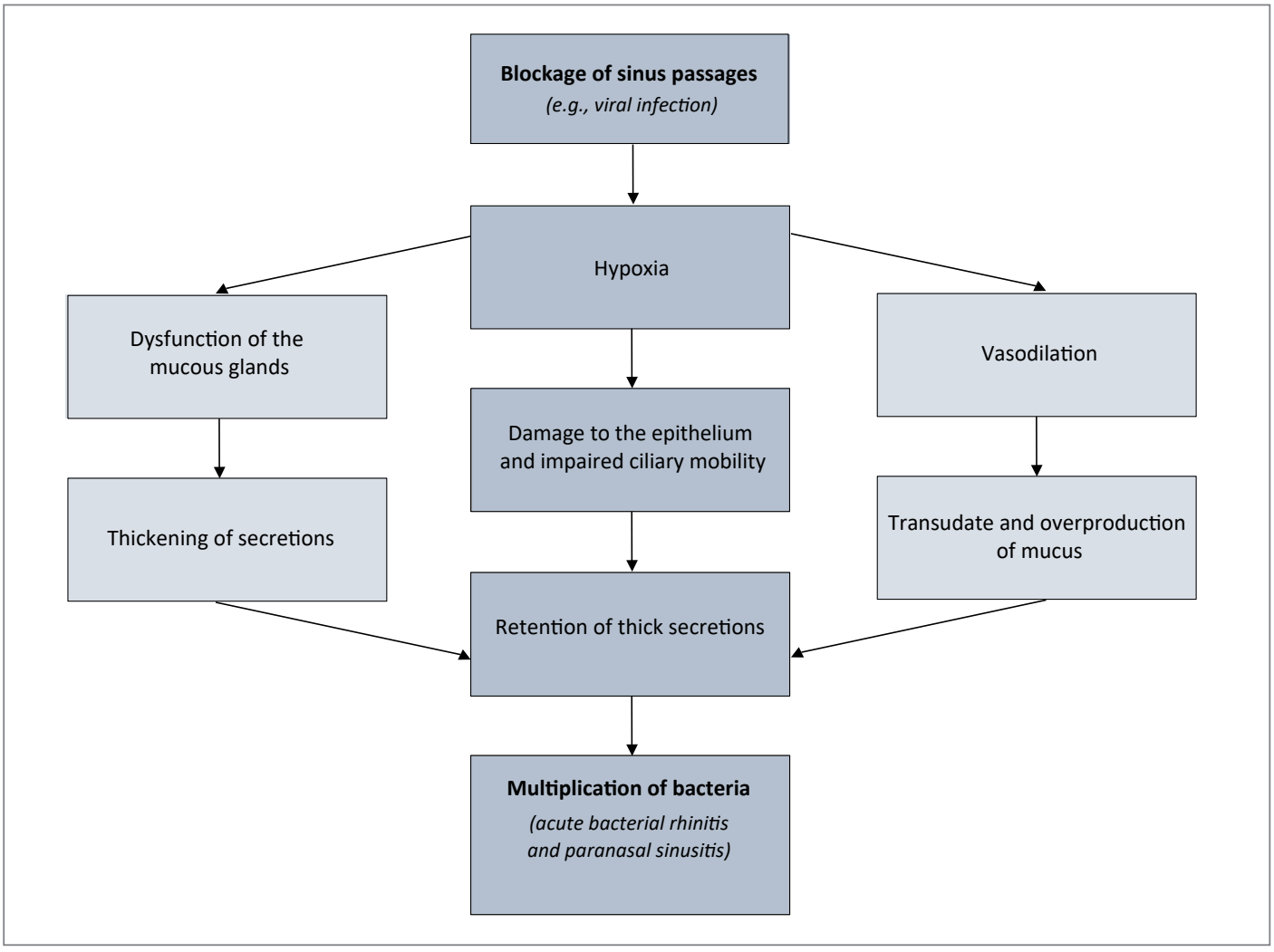

Fig. 1. Pathophysiology of rhinosinusitis.

ACUTE RHINOSINUS (ARS) IN ADULTS

Acute rhinosinusitis (ARS) in adults is defined as a sudden onset of 2 or more of the symptoms listed below, one of which should be nasal obstruction or nasal discharge (anterior/posterior nasal drip), lasting less than 12 weeks [1]:

- nasal obstruction,
- nasal discharge (anterior/posterior nasal drip),
- pain/sensation of increased pressure the face,
- impairment/loss of smell.

The EPOS 2020 document [1] additionally emphasizes the following definitions:

1. Common cold, i.e. acute viral maxillary rhinosinusitis with a duration of less than ten days;

2. Acute postviral sinusitis, where symptoms persist for more than 10 days (but less than 12 weeks) or symptoms worsen over the following 5 days;

3. Acute bacterial sinusitis defined as the presence of at least three of the following symptoms:

   - change in the color of the secretion,
   - localized severe pain,
   - fever above 38 degrees,
   - increased concentration of C-reactive protein (CRP) /elevated erythrocyte sedimentation rate (ESR),
   - deterioration after initial improvement.

EPIDEMIOLOGY OF ACUTE RHINOSINUSITIS

Acute rhinosinusitis (ARS) affects 6–15% of the population annually and is most often caused by a viral infection. The Recommendations for the Treatment of Out-of-Hospital Respiratory Infections [2] issued by the National Institute of Health include recommendations for the treatment of ARS. The authors of the Recommendation emphasize that ARS is initiated by a viral infection, in particular: rhinoviruses, coronaviruses, RS viruses, influenza and parainfluenza as well as adenoviruses [2]. Bacterial infection is a consequence of viral infection and

develops only in 0.5–2% of cases [2]. ARS usually is usually a self-limiting disease; however, it can lead to life-threatening complications [1, 2].

PATHOPHYSIOLOGY OF ACUTE RHINOSINUSITIS

In the first, vascular phase of inflammation, viral ARS is manifested by hyperemia and swelling of the nasal mucosa and paranasal sinuses, followed by abundant exudate. Clinically, we observe swelling of the nasal mucosa and paranasal sinuses (the cause of nasal congestion), followed by abundant discharge of watery discharge from the nose (possibly post-nasal drip responsible for the cough). This initial phase, usually lasting 5–10 days, is referred to as hyperemic-edematous-exudative.

Postviral ARS corresponds to the second, so-called cellular phase of the disease, which is clinically manifested by leakage of thick mucus discharge from the nose (also discolored) and possibly cough.

ARS is a disease of complex pathophysiology, the main components of which include inflammatory edema of nasal and sinus mucosa, narrowing of the sinus passages and reduced activity of the mucociliary system [1, 2]. Viral infection leads to damage of the ciliary epithelium, release of proinflammatory cytokines and swelling of the mucous membranes [1, 2]. Influenza viruses and adenoviruses possess the ability to damage epithelial ciliated cells of the mucous membranes, while rhinoviruses and coronaviruses provoke transient ciliary dysfunction. Cytokines and mediators of the inflammatory response: increase vascular permeability, induce edema of the mucous membrane, increased production of secretions and disruption of mucociliary transport [1, 2]. This, in turn, leads to impairment of sinus passages' patency, impaired ventilation of the sinuses and retention of secretions within the paranasal sinuses.

Fig. 1. presents a scheme of dysfunction involving the nose and sinuses in the course of ARS.

The authors of EPOS 2020 emphasize that there is a growing amount of experimental data confirming that nasal epithelium is the main entry route for respiratory viruses, as well as an active element of an initial response to viral infection. The inflammatory cascade initiated by nasal epithelial cells causes damage to the mucosa of the nose and paranasal sinuses, leading to swelling, excessive mucus production and obstruction of the sinus passages, resulting in postviral and even bacterial ARS [1].

TREATMENT OF ACUTE RHINOSINUSITIS

Treatment of acute viral rhinosinusitis (common cold)

Given viral etiology, lack of effective prevention method (vaccination) or effective causal treatment of ARS, treatment is focused on control of symptoms.

The treatment regimen for ARS [1] is presented in Fig. 2.

In the first, viral, phase of ARS/common cold, treatment is usually based on the so-called self-medication, possibly advised by a pharmacist. In the absence of symptoms of acute bacterial rhinosinusitis (ARBS) – Fig. 2., symptomatic agents typical for viral infections of the nose are used, i.e.:

- alpha mimetics (e.g., xylometazoline, intranasal oxymetazoline or oral pseudoephedrine) – no longer than 10 days,
- non-steroidal anti-inflammatory drugs,
- zinc,
- vitamin C,
- 0.9% NaCl – for rinsing or spraying of the nasal cavities.

At this stage of ARS, the authors of the EPOS documents [1] and national recommendations [2] emphasize the need to avoid antibiotic therapy.

TREATMENT OF POSTVIRAL ACUTE RHINOSINUSITIS

In postviral acute rhinosinusitis (when symptoms last more than 10 days or increase in severity after 5 days) it is recommended to use anti-inflammatory agents – intranasal glucocorticoids [1, 2] (Fig. 2.). The authors of EPOS 2020 [1] also list phytotherapy among the treatments used in postviral ARS.

Drugs used to treat postviral ARS according to EPOS 2020 [1]:

- intranasal glucocorticoids,
- alpha mimetics (less than 10 days),
- phytotherapy (herbal medicines),
- 0.9% NaCl – for rinsing or spraying nasal cavities,
- avoiding antibiotic therapy.

In the Polish Recommendations [2] for the treatment of out-of-hospital respiratory infections (from 2016), the authors refer to the 2012 EPOS document with regard to the treatment of ARS and cite that phytotherapy, 2 preparations in particular, is recommended: „The most convincing were studies using geraniums and myrtol, but not so much that they were included in the recommendations". Recommendation No. 3 [2] states: „In the postviral phase of Acute Rhinosinusitis, secretolytic herbal drugs [BII] may be used".

In the latest guidelines for the treatment of rhinosinusitis – EPOS 2020, the above-mentioned preparations were among the recommended treatments for ARS.

The EPOS 2020 document recommends plant-based drugs for the treatment of postviral ARS in order to reduce the severity of symptoms with class Ib recommendations [1]. The authors of EPOS 2020 [1] indicate that there are only a few randomized, double-blind, placebo-controlled trials conducted to evaluate the effectiveness of phytotherapy in the treatment of ARS, which is not representative of the full spectrum of herbal drugs used to

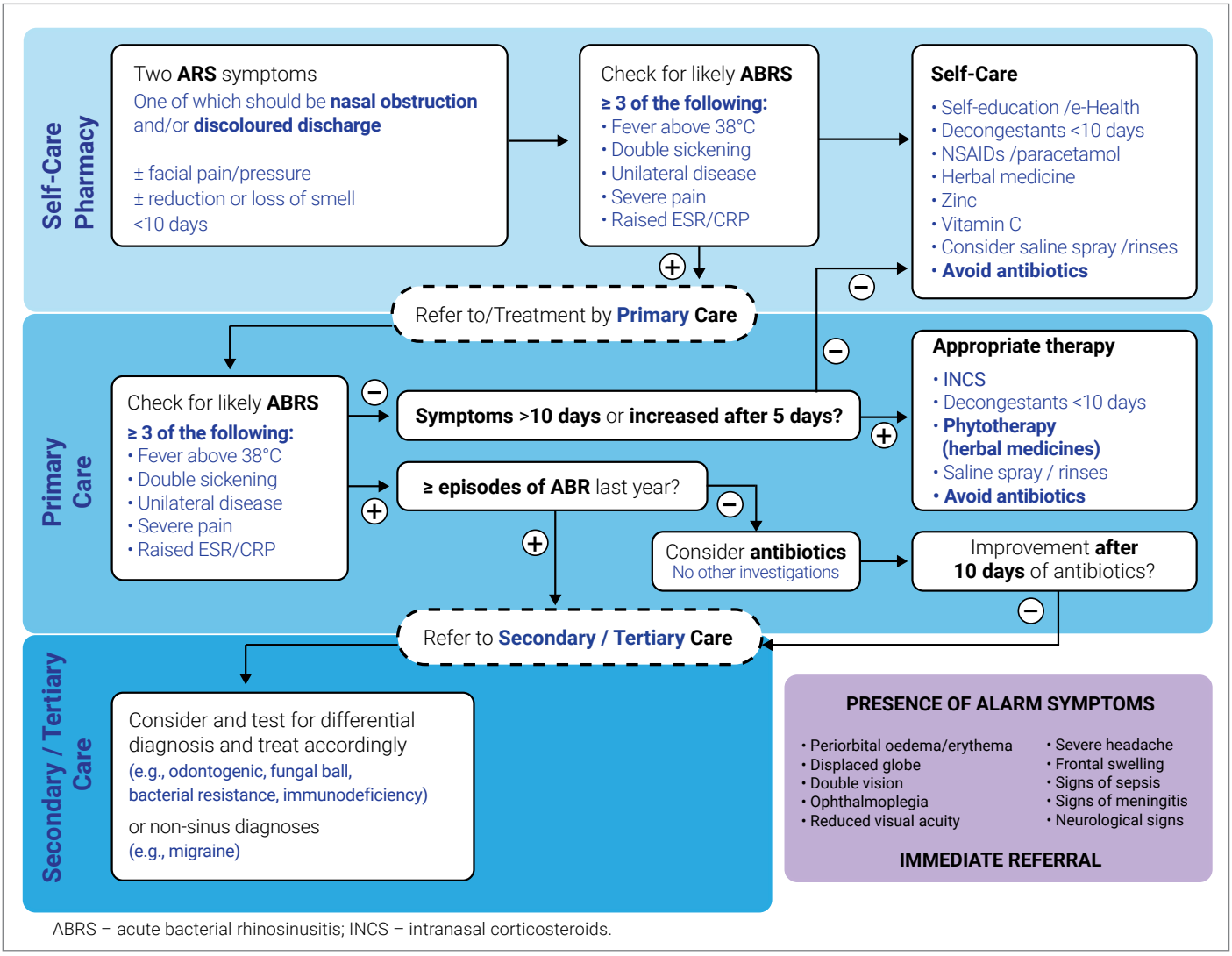

Fig. 2. Treatment regimen for ARS according to EPOS 2020 [1].

treat ARS. However, they point out that there is still no systematic review of publications analyzing the use of phytotherapy in ARS.

The EPOS document cites 2 publications on the use of eucalyptus oil extract with anti-inflammatory properties [4, 5]. The first study by Kehrl W. et al. included 302 patients with symptoms of viral rhinosinusitis and contained a placebo group [4]. In a second study by Tesche S. et al., the symptoms of patients with viral ARS who used eucalyptus oil extract were compared with an alternative herbal preparation [5]. In both studies, there was a greater reduction in patient symptoms and rhinoscopy results in the eucalyptus oil group than in the control group after seven days of treatment. Based on this, it can be concluded that eucalyptus oil extract has a significant effect on the symptoms of viral ARS without significant side effects.

The EPOS 2002 document also cites the publication by Federspil P. et al. [6], in which 3 groups of patients with ARS were examined in a double-blind randomized study with a placebo group. In this study, 109 patients took Myrtol (containing a distillate from a mixture of rectified eucalyptus essential oils, sweet orange, myrtle and lemon) for 6 days at a dose of 300 mg, 4 times a day. The second group consisted of 110 patients using an unregistered essential oil preparation and the third group included 111 patients taking placebo. All patients also received xylometazoline. Myrtol, as a standardized preparation, and another essential oil (unregistered) were found to be significantly better than placebo in reducing ARS symptoms. After treatment of acute rhinosinusitis with Myrtol, a lower proportion of patients required antibiotics (12.60% in the placebo group *vs.* 7.3% in the Myrtol group). Tolerance was slightly better for standardized Myrtol compared to essential oil [6].

In this publication, we present a fragment of the original table 1.4.2 (page 23 epos 2020) [1], where the drug we discussed, available in Poland since 2021, has obtained, according to the authors of EPOS 2020, the level of recommendation Ib in the treatment of acute postviral ARS (Tab. I.). Only glucocorticoids (intranasal and systemic) achieved a higher level of recommendation – Ia. ARS is one of the most common reasons for taking antibiotics and limiting their use is currently extremely important [1, 2]. All current recommendations indicate „avoiding antibiotics" in the treatment of viral and postviral ARS (Fig. 2.).

Tab. I. Treatment evidence and recommendation for adults with acute post-viral rhinosinusitis.

THERAPY	LEVEL OF EVIDENCE	GRADE recommendation
Herbal medicine	Ib	Some herbal medicines like BNO1016 tablets and Pelargonium sidoides drops and Myrtol (and other essential oil) capsules have significant impact on symptoms of acute postviral rhinosinusitis without significant adverse events.

PHYTOTHERAPY (HERBAL MEDICINES)

Currently, the pharmaceutical industry is increasingly interested in the search for new drugs among secondary plant metabolites. Natural products have been and will continue to be an important source of pharmacologically active compounds, and this interest is growing due to the failures of alternative methods of drug development.

MEDICINES *VS.* DIETARY SUPPLEMENTS

A discussion regarding differences between a medicinal product and a dietary supplement and the widespread use of the latter has been electrifying the community of doctors and pharmacists for many years. A reflection of this may be the report „Allowing dietary supplements to be marketed" [7] published by the Supreme Audit Office in 2017, which demonstrated that knowledge among Poles on this subject is alarmingly low. In a study conducted by TNS Polska in 2014 [8], it was shown that 25% of respondents cannot define the term „dietary supplement", and only 27% of respondents showed correct knowledge of it. An inexplicably large group, as many as 41% of respondents, attributed medicinal properties to dietary supplements that these products do not have, and 50% said that they are controlled same as drugs. Just over ⅓ of the respondents believed that supplements are checked for effectiveness, additionally mistakenly considering the supplements as „vitamins" (31%) or „minerals" (8%). According to the Act on Food and Nutrition Safety of 25 August 2006 [9], a dietary supplement is: „a food whose purpose is to supplement a normal diet, being a concentrated source of vitamins or minerals or other substances exhibiting nutritional or other physiological effect, simple or complex, marketed in a form that allows dosing as capsules, tablets, dragees and other similar forms, powder sachets, liquid ampoules, dropper bottles and other similar forms of liquid and powder intended to be consumed in small, measured unit quantities, excluding products possessing characteristics of a medicinal product as defined by the pharmaceutical law".

In accordance with the provisions of this Act, a dietary supplement is allowed to be marketed in Poland by the Chief Sanitary Inspector on the basis of the submitted application and a proposed draft of a label. No quality control, durability test results or testing for possible drug interactions apply. Supplements are not subject to pharmaceutical supervision and are also not monitored for possible side effects.

In Polish legislation we use the concept of a medicinal product. Its exact definition can be found in the Act of 6 September 2001. Pharmaceutical law [10]: „a medicinal product is a substance or mixture of substances presented as having the properties of preventing or treating diseases that occur in humans or animals or administered for the purpose of making a diagnosis or to restore, correct or modify physiological functions of the body through pharmacological, immunological or metabolic action".

Thus, the very analysis of the definition the concept of a supplement *vs.* medicinal product shows that the former is a food product, consumption of which only brings additional health benefits. These benefits consist of providing nutrients or other substances with nutritional or physiological effects in a concentrated form. Since the indication for their use is limited only to maintaining the balance of the body, they cannot be attributed the property of preventing disease or, even more so, therapeutics. Nor is it permissible to invoke such properties.

According to the pharmaceutical law, medicinal products are subject to registration at the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Pharmaceutical legislation provides for the control of the compliance of the final drug with the standards established for it. This obliges manufacturers to check the quality of raw materials used for the production of pharmaceutical preparations and to control both the production process as well as the final product. The medicinal product is under constant supervision o f the Chief Pharmaceutical Inspector. Side effects are also monitored as pharmacies, hospitals and doctors are obliged to them report to the Pharmaceutical Inspectorate [10].

It is particularly noteworthy that prescription medicines as well as over-the-counter drugs in combination with dietary supplements may cause unspecified adverse events, the outcomes of which are difficult to predict and can even be dangerous.

Therefore, there is a definite need to consult the ingested supplements with a doctor or a pharmacist with regard to possible interactions with concomitant medications.

An overview of the bioactive compounds: *Citrus sinensis*, *Citrus limon, Eucalyptus globulus Labill* and *Myrtus communis L* can constitute a valuable source of information for many key therapeutic areas.

CITRUS LIMON

Due to the great popularity and documented profile of pharmacological action, the chemical composition of *C. limon* fruits has been intensively studied for years and is well understood. Thus, the most important phytocompounds have been identified not only in the whole fruit, but also separately in the pericarp, juice, pomace and extremely important essential oil. Chemical compounds found in leaves and fatty oil extracted from the seeds are also identified. Due to the large number of varieties, the phytochemical composition of *C. limon* is not constant.

The most important group of compounds, next to ascorbic acid, determining the biological activity of both fruit and juice, are flavonoids, such as: flavonones, flavones, flavonols and their derivatives [11]. Compared to other species, *C. limon* has the highest eriocitrin content [11].

Another important group of bio compounds found in both juice as well as the fruit are phenolic acids. The juice contains mainly two such compounds – ferulic and sinapinic acid and their close analogues. Moreover, in fruits one can also find: coumarin compounds, carboxylic acids, carbohydrates, as well as amino acids, type B vitamins and, most importantly, ascorbic acid [12–15].

Another interesting group of compounds found in *C. limon* fruits are limonoids – highly oxidized secondary metabolites with polycyclic triterpenoid skeletal structures: limonin and nomilin [16].

Analysis of macronutrients in *C. limon* fruits demonstrated the presence of calcium (Ca), magnesium (Mg), phosphorus (P), potassium (K) and sodium (Na) [15] in the pulp and skin. Moreover, a number of fatty acids have been identified in *C. limon* seeds, together with tocopherols and carotenoids [13, 14].

As in the case of *Eucalyptus globulus Labill.*, the wealth of phytocompounds and macroelements listed and endowed with high biological activity determines a number of beneficial activities that have been practically applicable in medicine and pharmaceuticals for years. Noteworthy is the antioxidant activity of flavonoids from *C. limon* – hesperidins and hesperetine – which was not only limited to their antiradical activity, but also strengthened antioxidant cellular protection through the ERK/Nrf2 signaling pathway [17]. The antioxidant effect is shown by vitamin C itself, which not only prevents the formation of free radicals, but also reduces damage to DNA, lipids and proteins. In addition, ascorbic acid inhibits nitrosation reactions and is an inhibitor of angiogenesis [18].

The activity of hesperidin metabolites and their synthetic derivatives in reducing inflammation, including NF-κB, iNOS and COX-2, as well as markers of chronic inflammation was confirmed in a series of *in vitro* and *in vivo* studies, [17]. In an animal model, the essential oil of *C. limon* (30 or 10 mg/kg p.o.) exhibited anti-inflammatory effects, reducing cell migration, cytokine production, and extravasation of carrageenan-induced protein. The authors of the report postulate that anti-inflammatory effect of the oil is probably due to the high concentration of d-limonene [19]. Anti-inflammatory effects were also the subject of a study in which *C. limon* oil was shown to moderately inhibit soy 5-lipoxygenase (5-LOX) with an IC_{50} value of 32.05 μg/ml [20].

C. limon essential oils have been the subject of studies in which their antibacterial effect against Gram(+) bacteria – *Bacillus subtilis* (minimum inhibitory concentration MIC – 2 mg/mL), *Staphylococcus capitis* (MIC 4 mg/mL), *Micrococcus luteus* (MIC 4 mg/mL) and Gram(–) *Pseudomonas fluorescens* (MIC 4 mg/mL), *Escherichia coli* (100% inhibition) has been demonstrated [20, 21]. The same type of oil had an inhibitory effect against *Staphylococcus mutans* (MIC 4.5 mg/mL) – it effectively reduced the adhesion of *S. mutans* to the glass surface, with adhesion inhibition rates (AIR) from 98.3% to 100%, while on the surface of saliva-coated glass, AIR values ranged from 54.8% to 79.2%. In addition, it effectively reduced glucosyl transferase (Gtf) activity and Gtf transcription in a dose-dependent manner [22]. The biocomponents of *C. limon* essential oil, such as d-limonene, β-pinene and citral, have shown inhibitory effects against *Aspergillus niger* (MIC 90 μL/mL at 70°C), *Saccharomyces cerevisiae* (MIC 4 mg/mL) and *Candida parapsilosis* (MIC 8 mg/mL) [20, 23]. Other studies have confirmed that *C. limon* essential oil promoted a 100% reduction in the growth of *Candida albicans* [24], and at a concentration of 0.05% inhibited herpes simplex replication at a rate of 33.3% [25].

CITRUS SINENSIS

C. sinensis represents the largest group among citrus varieties grown worldwide, accounting for about 70% of the total annual production of *Citrus species* [26].

C. sinensis is a rich source of secondary metabolites, which are responsible for the pharmacological activity attributed to this plant. Several types of chemical compounds have been identified in the fruits, peel, leaves, juice and roots of *C. sinensis*, including flavonoids [27–29, 34], steroids [29], hydroxyamides, alkanes and fatty acids [29], coumarins [30], peptides [31], carbohydrates [32], carbamates and alkylamines [33], carotenoids [34], volatile compounds [35] as well as potassium (K), magnesium (Mg), calcium (Ca) and sodium (Na) macroelements [36].

Cold-pressed terpeneless oil (CPT) obtained from *C. sinensis*, dissolved in ethanol or dimethyl sulfoxide (DMSO), showed a minimum inhibitory concentration (MIC) of 0.3% and 0.25% v/v for *Listeria monocytogenes* and 1% v/v for *Salmonella typhimurium*. Dispersion systems, based on the same solvents, showed mean MIC values of 0.75% v/v for *Lactobacillus plantarum* [37]. The inhibitory effect of CPT oil on the growth of six strains of *Staphylococcus aureus* was examined by the disk diffusion method (10 μL solution). In this way, it was shown that the bacterial growth inhibition zone for methicillin-sensitive strains, methicillin-resistant strains, and strains of medium resistance to methicillin and vancomycin was respectively: 31.50 ± 3.02 mm; 65.83 ± 3.76 mm; 76.67 ± 4.08 mm and 32.50 ± 2.74 mm [38].

Essential oil, containing eucalyptol (1,8-cineol), showed MIC90% ≥ 10% (v/v) against *P. aeruginosa* [39]. In a study by another research group, it was found (disk-diffusion method – 0.1 mL) that *C. sinensis* oil showed a varying, but small inhibitory effect on development of: *E. coli* (18 ± 2 mm), *L. monocytogenes* (27 ± 2 mm), *Bacillus cereus* (19 ± 2 mm) and *Staphylococcus aureus* (14 ± 3 mm). Fractions isolated from sweet orange oil: decanal (73.36%), octanal (78.12%) or linalool (90.61%), showed an inhibitory bactericidal effect against: *E. coli* (MIC 100–25 μg/mL; MBC 200–50 μg/ml), *S. aureus* (MIC 100–50 μg/ml; MBC 200–100 μg/ml), *Saccharomyces cerevisiae* (MIC 100–6.25 μg/ml; MBC 200–25 μg/ml), *Aspergillus niger* (MIC 50 μg/ml; MBC 200–100

μg/ml) and inactivity against: *Penicillium citrinum* [40]. A mixture (1:1 v/v) of essential oils of the *C. sinensis* and *C. bergamia* varieties showed inhibitory activity at MIC values of 0.25–0.5% (v/v) and a minimum inhibitory dose (MID) of 50 mg/L against vancomycin-sensitive and vancomycin-resistant *Enterococcus faecium* and *E. faecalis*, respectively. The dominant components of the mixture were limonene (45%–73%), citral (0.7%–3%) and linalool (0.5%–15%) [41, 42]. Terpene oil, obtained from the essence of *C. sinensis* (10 μL), was inhibited the development of eleven strains/serotypes of Salmonella: *S. enteritidis*, *S. senftenberg*, *S. senftenberg*, *S. tennessee*, *S. kentucky*, *S. heidelberg*, *S. montevideo*, *S. michigan*, *S. typhimurium* and *S. Stanley* with a diameter of inhibition zone of 29.2 ± 3.7 mm. The most dominating compound in the extract studied (94%) was d-limonene, followed by myrcene, constituting about 3% of the substance [43]. Similarly, acetone and hexane extracts of *C. sinensis* leaf showed inhibition zones with a diameter of 27 mm for *Helicobacter pylori* [44]. And although the tested extracts were characterized by lower activity compared to clarithromycin (0.05 μg/mL), the above results clearly indicate a wide antibacterial spectrum, which justifies their use as antibacterial agents.

The total antioxidant activity of raw *C. sinensis* juice, the Moro variety, was assessed based on its ability to sweep away the model radical DPPH, OH• ABTS+ and reduce iron cations. The juice of this variety was found to effectively sweep away ABTS+ radical cations, reaching up to 64% extinction, equivalent to 14.30 μM of the reference antioxidant Trolox (TE). It was also able to sweep away DPPH radicals with antioxidant power equivalent to 14.39 ± 0.19 μM TE and eliminate about 87% of the hydroxyl radicals generated at 16.40 μM TE. The above antioxidant activities are attributed to the presence of five C-glycosyl flavones, quercetin and one O-glycosidic flavone [45].

Significant antioxidant activity of the juice of five different varieties of *C. sinensis* is also confirmed by amperometric studies using an innovative cytochrome c based biosensor [46]. *C. sinensis* seed extract showed antioxidant activity in DPPH radical-reducing and scavenging assays in studies that used gallic acid (IC50 = 29.5 μM) as a control standard [47].

The main groups of flavonoids found in the studied fractions of methanol extract of orange peel of the Navel variety (including flavedo and albedo parts) were: polymethoxylated flavones, O-glycosylated flavones, C-glycosylated flavones, O-glycosylated flavonols, O-glycosylated flavonones and phenolic acids with their ester derivatives. At the same time, the main flavonoid glycoside, found in the orange peel, turned out to be hesperidin. Antioxidant activity of the material was assessed using DPPH test and luminol chemiluminescence test, induced by Co(II)/EDTA. The obtained results showed that the tested methanol extracts have moderate antioxidant activity compared to the activity observed for free aglycones diosmetin (EC50 71.79 ± 13.58 mg) and hesperetin (EC50 29.18 ± 2.80 7 mg). The experiment used quercetin as a control (EC50 = 0.06 mg quercetin/mg DPPH), and tested aglicones showed significantly higher OH• sweeping activity than quercetin [48]. Raw *C. sinensis* juice showed anti-radical effect of DPPH at 84.81% at a concentration of 100 μg/mL. The study used ascorbic acid as a control, which exhibited an anti-radical effect of 96.36% DPPH [49].

Phenolic extracts obtained from the peel of *C. sinensis* had a great ability to capture DPPH, ABTS+ (6.09 mmol/TEAC g) and iron-reducing antioxidant properties (FRAP) (71.99 mg/GAE 100 g) [50]. Acetone-water extract obtained from the fresh, edible part of the fruits of the red orange of the Tarocco variety, showed an intracellular antioxidant activity of 85% in Caco-2 cells at 50 mg /mL. The tested extract showed much higher antioxidant activity than controls – gallic acid and vitamin C [51]. Methanol and ethanol extracts of *C. sinensis* peel showed significant free radical capture activity generated by ABTS+, respectively: 55.8% and 60.7% and DPPH capture activity, amounting to 70% and 80% respectively – water (20-150 μl) and ascorbic acid were used as controls [52].

EUCALYPTUS GLOBULUS LABILL

Essential oil obtained from *Eucalyptus spp.* is one of the 18 most often bought essential oils worldwide. Among them, the most important source of this raw material is *E. globulus Labill* [53]. The key phytonutrient of this plant is eucalyptol (1,8-cineol), a monoterpene ether with an intense spicy-herbal odor [53–57]. Due to the wide range of biological activities, eucalyptus leaf essential oil and *E. globulus Labill* itself draw the attention of many research teams. Intensive research allowed the determination of other bioactive ingredients in its various parts. Among them, one can find a number of phytocompounds that – although to a lesser extent – give this plant therapeutic properties. The presence of tannins, saponins, terpenoids, glycosides, alkaloids, phenolic compounds, steroids, cardiac glycosides, terpenes, reducing sugars, carbohydrates, resins, acid compounds and flavonoids was demonstrated thanks to this work [56, 58–61]. Among those mentioned, particularly noteworthy are phenols, which are responsible for antioxidant activity [56, 58–61] and triterpene compounds with other, significant pharmaceutical applications [62–64]. The increasing use of antioxidants on a global scale motivates industrial pharmaceutical centers to intensify the search for alternative antioxidants of plant origin to avoid the adverse effects of synthetic antioxidants [65]. Therefore, the antioxidant potential of various parts of eucalyptus plants (leaves, fruits, roots), as well as their essential oils, is an extremely interesting area for medics to take advantage of in order to reduce the adverse events caused by oxidative stress [54–56, 60, 61, 67, 68].

Another area of application of *E. globulus Labill* leaf oil in medicine and pharmacy is associated with its antibacterial efficacy against Gram-positive and Gram-negative bacteria [53–55, 60, 66], as well as an evident anti-inflammatory effect [60, 67, 68].

MYRTUS COMMUNIS L

Myrtus communis L is a medicinal plant that has played a significant role in medicine and pharmacy, as well as food and cosmetic industries for years. Most of its applications, previously known

and utilized in traditional medicine, have been confirmed by scientific experimental studies, including antimicrobial, antioxidant and anti-inflammatory effects presented in this publication.

The main components of *M. communis* leaves are flavonoids, such as galloyl derivatives of catechins and gallocacechins, as well as myricetin derivatives [69]. There are also phenolic acids (caffeic, ellagic and gallic acids) and flavonoids, quercetin derivatives 3-O-galactoside quercetin and quercetin 3-O-rhamnoside present in smaller quantities. Moreover, 4 hydrolyzable tannins, 2 polyphenolic compounds and 4 myricetin glycosides have been isolated [70]. The main terpenoids and their derivatives found in the essential oils of *M. communis L* leaves were: α-pinene, α-terpineol, linalool, 1,8-cineol (eucalyptol), geranyl butyrate, geraniol, caryophyllene oxide and neryl acetate [71]. Five sesquiterpene-based meroterpenoids with 3 new types of skeletons [1, 2, 3, (+)-4 and (–)-4] were also isolated from the leaves of *M. communis* [72].

Essential oils obtained from the leaves of *M. communis L* have shown promising but variable activity against laboratory microbial strains, including 6 Gram(+): *Staphylococcus aureus*, *Micrococcus luteus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Listeria monocytogenes* and 4 Gram(–): *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Campylobacter jejuni* [73]. Similarly, promising results have been the subject of studies of antibacterial activity in strains: *E. coli*, *S. aureus*, *P. aeruginosa*, *P. vulgaris*, *P. mirabilis*, *K. aerogenes*, *S. typhi* and *S. shigie* [74].

Alcohol extract of *M. communis* was shown to be effective against selected *Escherichia coli* isolates producing extended-spectrum beta-lactamase [75]. In addition, myrtle oil showed strong antimicrobial activity against *Helicobacter pylori* [76] and strains of *Mycobacterium tuberculosis* [77]. In parallel experiments, it has been shown that the largest share of antimicrobial properties of myrtle oil is attributed to α-pinene, 1,8-cineol (eucalyptol), α-pinene and limonene [78].

80% ethanol leaf extract of *M. communis L* showed anti-inflammatory effects in animal models. Isolated components of the extract also had similar properties – e.g., unprenylated phloroglucinol derivatives [79]. Treatment with *M. communis L* ethanol extract reversed all biochemical indicators as well as histopathological changes caused by acetic acid. The protective effect of the studied extract resembled that of a sulfonamide drug, sulfasalazine. The anti-inflammatory potential of myrtle oil was also assessed using an in vitro model of lipopolysaccharide-stimulated macrophages. Cell viability was assessed using mitochondrial oxidoreductive activity in an MTT test. The oil was able to significantly inhibit NO production without affecting cell viability [80].

Antioxidant activity has been the subject of a number of classical studies involving DPPH [81–83], β-carotene/linoleic acid system [82, 83], ABTS+ [84], iron(II) thiocyanate [83].

SUMMARY

All the essential oils in question have a similar or complementary phytochemical composition. As a result, it focuses the direction of pharmacological effects (among others) on anti-inflammatory, antioxidant and antimicrobial activity. Clinically, this results in: improving ciliary mobility and restoring proper mucociliary transport, reducing mucus density and facilitating its evacuation. Acute rhinosinusitis, both in viral and postviral phases, requires a special approach to a patient. Due to viral etiology of the disease and lack of causal treatment, it is necessary to use symptomatic agents that will reduce the burden of clinical symptoms, but also prevent complications. Most patients with ARS, reporting directly to an ENT specialist or referred by family doctors, expect the specialist to apply effective treatment, which in patient's opinion is often synonymous with antibiotic therapy. Taking into account the recommendations and treatment regimens in ARS, clearly indicating the need to avoid antibiotic therapy in acute viral and acute postviral rhinosinusitis, any new drug registered with an indication of alleviating the symptoms of acute upper respiratory tract infection can contribute to more effective treatment of ARS and avoidance of unnecessary antibiotic therapy.

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