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Recommendation for use of Sinupret extract in acute rhinosinusitis

Rekomendacja dla leku Sinupret extract w ostrych zapaleniach błony śluzowej nosa i zatok przynosowych

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ABSTRACT: Acute and chronic rhinosinusitis is the most common problem encountered in ENT practice. Nearly all cases of acute rhinosinusitis are of viral background. Further course of the disease is determined by the condition of mucosal membranes, systemic immune strength, virulence of the infectious agent and the morphology of paranasal sinuses. Medications used in acute rhinosinusitis provide symptomatic treatment, their effect being aimed at reduction of inflammation and swelling. Products obtained from medicinal plants may provide an alternative to these medications. In vitro studies have shown that these products demonstrate anti-inflammatory, immunostimulating, anti-edemic, and antiviral effects. With the market placement of Sinupret extract, the armamentarium of therapeutic has been extended by a concentrated product characterized by strength comparable to that of synthetic analgesic and anti-inflammatory drug as well as by additional, documented antiviral effect. The article discusses the composition of Sinupret extract, the mechanisms of action of its active substances, and the results of preclinical and clinical studies of Sinupret and Sinupret extract.

KEYWORDS: acute rhinosinusitis, sinupret, sinupret extract, bioactive ingredients, mechanism of action, documented therapeutic effect

STRESZCZENIE: Ostry i przewlekły nieżyt nosa i zatok przynosowych jest najczęstszym problemem w praktyce lekarza otolaryngologa. Niemal każdy przypadek nieżytu ostrego ma tło wirusowe. Dalszy przebieg choroby uwarunkowany jest jakością błon śluzowych, siłami odpornościowymi ustroju, zjadliwością wirusa oraz morfologią zatok przynosowych. Stosowane w nieżycie ostrym leki mają charakter objawowy, a ich efekt nakierowany jest na wygaszenie stanu zapalnego i obrzęku. Alternatywą wobec tych leków są preparaty przygotowane na bazie roślin leczniczych. W badaniach in vitro wykazują one działanie przeciwzapalne, immunostymulujące, przeciwobrzękowe i przeciwwirusowe. Wobec wprowadzenia do sprzedaży preparatu Sinupret extract arsenał środków terapeutycznych poszerzył się o skoncentrowany lek, o sile działania porównywalnej z działaniem syntetycznych leków przeciwbólowych i przewciwzapalnych, mający dodatkowo udokumentowane działanie przeciwwirusowe. W pracy omówiono skład preparatu Sinupret extract, mechanizmy działania jego substancji czynnych oraz wyniki badań przedklinicznych i klinicznych z udziałem leków Sinupret i Sinupret extract.

SŁOWA KLUCZOWE: ostry nieżyt nosa/zatok przynosowych, sinupret, sinupret extract, składniki bioaktywne, mechanizm działania, udokumentowane działanie lecznicze

INTRODUCTION

A vast majority of about 80% of all ENT patients present with conditions of nasal cavities and/or paranasal sinuses [1]. These conditions are characterized by transient or permanent disturbance of the structure and function of mucosal membranes due to acute or chronic infections of the upper respiratory tract.

A significant problem associated with acute rhinosinusitis consists in excessive, overly extensive inflammatory reaction incommensurate to the risk posed by "commonplace catarrhal infection". This hyperactivity results in excessive swelling of the mucosal membrane. This initially defensive systemic reaction is aimed at inhibition of the spread of the infections; however, it also leads to prolonged and excessively strong blockade of sinus openings. This condition becomes in fact another link in the pathogenetic chain, leading to obstruction of sinus cavities and consequently inducing sinusitis. Due to the persistence of the block of anatomically closed cavities with simultaneously increased production of mucus, accumulation of mucus occurs and is followed by the growth of bacterial cultures [1]. In principle, one might propose that the blockage of paranasal sinuses is the start of a vicious circle progressing according to the following scheme: viral infection → swelling → blocked opening → accumulation of secretion → bacterial growth → exacerbation of inflammation → exacerbation of swelling → blocked opening → etc. In a vast majority of cases, the background of acute sinusitis usually consists of viral infection. Concomitant bacterial infection may develop in cases of reduced immunity and lack of natural anatomical barriers such as properly functioning mucosal membranes [1]. In this mechanism, even minute anatomical anomalies may result in chronic sinusitis.

Therefore, a crucial element of the treatment of acute conditions consists in reducing the intensity of inflammation and nasal mucosal swelling. Conventional countermeasures include topical administration of α-mimetics to decongest the sinus openings and steroids, also applied topically, to reduce inflammation. Unfortunately, patients tend to extend the duration of treatment since its discontinuation leads to a difficult to accept transient exacerbation of swelling and reduced nasal patency, particularly during the night. Extended treatment leads to hyperactivity of blood vessels within nasal mucosa and has an adverse effect on mucosal quality; this condition is referred to as rebound rhinitis (*rhinitis medicamentosa*) [2].

Natural-based products may provide an alternative or supplementation of the conventional treatment with α-mimetics and steroids. Natural-based products are particularly recommended in outpatient setting due to their safety and less common occurrence of adverse effects [3]. Phytopharmaceuticals are accepted in evidence-based medicine (EBM) on the basis of numerous clinical studies and meta-analyses. In today's medicine, phytopharmaceuticals are used as standalone agents in mild to moderate acute or chronic inflammations or as supportive drugs in all types of inflammations [4, 5].

CHARACTERIZATION OF THE PLANT SOURCES OF THE INGREDIENTS OF SINUPRET EXTRACT

Sinupret extract is a combination product containing extracts from gentian, primrose, dock, elderberry, and vervain [6].

Great yellow gentian *(Gentiana lutea L.)*

is a blooming perennial herb belonging to the family of *Gentianaceae* which comprises about 400 species. It grows in the mountain regions of central and southern Europe as well as western Asia [7]. A total of 29 species of the genus *Gentiana* are known in Europe, including 8 species occurring in Poland. Already in ancient times, the herb was used to produce gentian – a dye and a drug for external use. In addition, extracts of great yellow gentian are used as ingredients of oral preparations. Substances present in great yellow gentian were observed to exert beneficial effects in gastric disorders. They also present with anti-inflammatory, choleretic and diurectic effects [8, 9]. These properties of the extracts are mainly due to the presence of bitter secoiridoids including gentiopicroside, amarogentin, and swertiamarin, as well as xanthones such as isovitexin and isogentisin [10, 11]. Other properties of gentian extracts were also reported recently. Secoiridoid glycosides (aka bitter secoiridoids) [12, 13] exert their anticancer and antioxidative affects by inhibiting monoamine oxidase A and B as well as xanthine oxidase [11, 14-16]. Xanthones contained in gentian extracts exert antioxidative effects [17].

Primroses *(Primula L.)*

constitute a genus of plants from the family of *Primulaceae*. According to different taxonomical approaches, the genus encompasses about 400 to 500 species. They grow mainly in moderate climate areas of Europe and Asia, their habitats including meadows, rocky precipices and forests[7]. Cowslip (*Primula officinalis L.*) and true oxlip (*Primula eliator L.*) are common in Poland and are cultured as decorative plants while simultaneously being known for ages for their medicinal properties including decongestant, antibacterial, antifungal, anti-inflammatory, diaphoretic, diuretic, and spasmolytic effects. For these reasons, both plants are used in the treatment of upper and lower respiratory tract infections, alleviation of urinary tract inflammation and intestinal colic. The anti-inflammatory effects of the root and flower extracts are believed to derive from bioactive compounds includ-

ing salicylates, flavonoids, saponins, and phenolic glycosides [7, 18, 19, 20]. Cowslip extract was documented to exert secretomotor effects within the autonomic nervous system of the bronchial tree in rabbits, leading to significant increase in the production of mucous secretion within the bronchi [21]. Both the antifungal and the antibacterial activity of cowslip products are due to its content of triterpenic saponins.

Patience dock *(Rumex patientia L.)*

belongs to a genus comprising about 200 species from the family *Polygonaceae*. Plants of this family are widespread all over the world, particularly in moderate climate zones [7]. They are ruderal plants growing in anthropogenically disturbed areas which makes them very common in developed countries. Some species are edible and used as a vegetable while other species are treated as weeds. Extracts and concoctions of patience dock have been known in natural medicine for centuries due to their diuretic, laxative, antipyretic, anti-inflammatory, antifungal and wound healing-promoting activity [22, 23]. Dock leaves contain mineral salts (potassium, calcium, magnesium, iron), organic acids (malic acid, citric acid), flavonoids, proteins, sugars, tannins, carotene, vitamins B1, B2, C, K, and PP. Thus they have nutritional, health-promoting, as well as therapeutic properties. Biologically active compounds found in patience dock include flavonoids, anthraquinones, polyphenols, aromatic asters, terpenes, aldehydes, isoprenoids, ketones, steroids, and alcohols [22-24].

European elderberry *(Sambucus nigra L.)*

is a common species of a blooming perennial shrub widespread on the northern hemisphere [7]. Its fruits, rich in sugars (sucrose, fructose glucose) and organic acids (citric acid, malic acid, fumaric acid, and shikimic acid), present therapeutic properties [25-27]. Elderberry flowers are particularly rich in flavonoids, including anthocyanins and cyanidins, as well as glycosides [27-29]. These compounds are responsible for its attractive, most commonly blue/violet color. Other biologically active substances present in different parts of elderberry plants include quercetin and its glycoside derivatives rutinoside and glucoside with established anti-allergic and anti-inflammatory activity exerted by means of inhibition of enzymes involved in production of leukotrienes and prostaglandins as well as inhibition of mast cell degranulation [27].

Garden verbena *(Verbena hybrida, L.)*

grows in Eurasia and southern Africa. In Europe, it is most prevalent within the Mediterranean basin [7]. The plant has been used in traditional Chinese medicine for thousands of years [28, 29]. Extract and concoctions of garden verbena have antipyretic, anti-inflammatory, diuretic, diaphoretic, analgesic, myometrium-toning (prevention of postpartum uterine atony and support of the course of delivery), immunostimulating and neuroprotective (supportively in e.g. post-stroke rehabilitation) effects [32-34]. Active substances consist mainly of polyphenols, predominantly flavonoids, phenolic acids, phenylpropanoids, and iridoid glycosides [35, 36]. The anti-inflammatory effect observed for the 3% alcoholic extract and comparable to that of piroxicam as well as the analgesic effect comparable to that of the acetylsalicylic acid are considered to be due to the presence of iridoid glycosides [37]. Neuroprotective and immunostimulating effects are in turn considered to be due to the presence of phelylpropanoid glycosides: verbenalin and verbascozide [38, 39].

CHARACTERIZATION OF BIOLOGICALLY ACTIVE COMPOUNDS CONTAINED IN THE PLANT EXTRACT INGREDIENTS OF SINUPRET EXTRACT

Numerous therapeutic chemical substances listed in this second part of this article belong to the category of secondary plant metabolites, i.e. compounds of no importance for the plant structure or trophics i.e. Building blocks, energy sources, enzymes) being synthesized mainly to confer certain species-specific traits (color, aroma, flavor), perform protective (antifungal, antiparasitic, antiviral) as well as a signaling role (both within and outside the plant)[40]. Secondary plant metabolites can be divided into three main categories: terpenoids, non-protein nitrogen compounds, and phenolic compounds.

Terpenes

and their oxidized derivatives, i.e. terpenoids, are organic compounds with main skeletons consisting of varying numbers of five-carbon isoprene units (five-carbon hydrocarbon with two unsaturated bonds, empirical formula C_5H_8) with additional functional groups such as hydroxyl groups (-OH), ketone groups(=O), or heterocyclic rings (i.e. cyclic moieties containing at least one non-carbon atom). Terpenoids are important for plant cell metabolism as they are involved in the transfer of electrons and protons within the respiratory chain (plastoquinones and ubiqiunones), photosynthetic dyes (carotenoids, phytol), phytohormones, or cell wall components (phytosterols) [40].

NON-PROTEIN NITROGEN COMPOUNDS ARE MAINLY ALKALOIDS AND GLYCOSIDES

Alkaloids

are derived from amino acid precursors and contain nitrogen atoms within heterocyclic rings. They are usually toxic and

unpleasant in taste so as to protect the plant from herbivore animals. Alkaloids are usually present in herbaceous plants, although their presence was also discovered in animal organisms (sponges, insects, amphibians). Due to their strong pharmacological effects, alkaloids have been extensively researched and widely used in conventional medicine for many years (examples include morphine, quinine, or vinblastine).

Glycosides

are organic compounds consisting of a simple sugar moiety and a non-sugar fragment (aglycon) tethered to the sugar via an oxygen (–OR) or a nitrogen atom (–NR). The bond between the sugar and the aglycon moiety is referred to as glycoside bond. Glycosides are also a class of compounds widespread in nature. Similarly to alkaloids, some glycosides demonstrate strong pharmacological activity. Cyanogenic glycosides such as amygdalin are sources of hydrogen cyanide which, due to its properties, protects the plants from pests. Digitalis glycosides are well-known agents that support the cardiac function by exerting their effect on the sodium-nitrogen pump mechanism.

Phenetyl glycosides – phenylethanoids

are a class of glycosides featuring combination of a sugar, phenylethyl alcohol, and cinnamic acid derivatives. Thus, from the standpoint of classification of organic compounds they can also be viewed as esters (products of reactions between alcohols and organic acids). One of such compounds is verbascozide. It was documented to inhibit the activity of microorganisms, particularly *Staphylococcus aureus* [41], as well as to exert anti-inflammatory effects [42]. As enzyme-activating inhibitors of protein kinases C, (tertiary signal transducers), these compounds may strongly interfere with cytoplasmic signaling pathways and cellular metabolism [43], e.g. by exerting anti-oxidative and anti-inflammatory effects [44]. Scientific evidence is also available to support a relatively wide spectrum of their antibacterial activity [45].

Saponins

are a group of glycosides featuring triterpenic (i.e. consisting of 30 carbon atoms, or 6 isoprene units) aglycons. Saponins (such as primulasaponin A found in cowslip)are lipophilic and thus capable of affecting the structure of cellular walls to make them more permeable for various types of organic compounds, thus possibly exerting lethal effects on parasites and fungi [46]. They may also increase the secretion of lysozyme characterized by antibacterial activity [47]. The mechanism of anti-inflammatory effect of triterpenic saponins consists mainly in inhibition of enzymes involved in inflammatory response (phospholipase A2, cyclooxygenase, lipooxygenase, nitrogen oxide synthase, elastase) and inhibition of synthesis of prostaglandins and pro-inflammatory cytokines (TNF-α, IFN-γ, interleukins) [48].

Iridoids and secoiridoids

are terpene-based glycosides. Iridoids are derived from full monoterpenic iridane skeletons while secoiridoids are derived from cleaved iridane moieties. The best known representative of this class of compounds, currently the subject of extensive research, is oleuropein contained within olives. Due to the presence of two hydroxyl groups, iridoids may also be classified as polyphenols [49] which explains their strong anti-inflammatory and antioxidative effect.

Phenolic compounds

contain at least one aromatic (benzene) ring, at least one hydroxyl group and other substituents. Most phenolic compounds are built of phenylalanine and tyrosine amino acids. Phenolic compounds are divided into polyphenols (including flavonoids), other phenolic compounds (phenolic acids such as hydroxybenzoic and hydroxycinnamic acids), and phenolic alcohols.

Polyphenols

are a broad class of plant-derived organic compounds characterized by the presence of at least two phenolic rings and at least two hydroxyl substituents. Their precursors, phenylpropanoids, are derived from phenylalanine and consist of benzene rings and propanol chains. The common characteristic of all polyphenols is the ease of their involvement in redox reactions [50]. Main sources of polyphenols in human diet consist in fruit and vegetables as well as tea, coffee, red wine, chocolate, and beer.

Polyphenols include hydroxybenzoic acids, hydroxycinnamic acids, flavonoids, and isoflavonoids [50, 51].

Flavonoids

are a group of about 4000 aromatic organic compounds jointly referred to as vitamin P. They demonstrate antioxidative, anti-inflammatory, anticancer, antiatherosclerotic, antiaggregation, spasmolytic and diuretic activity in both *in vitro* and *in vivo* studies [52]. Thanks to the presence of hydroxyl groups, double bonds in positions C-2 / C-3, and carbonyl groups in position C-4, flavonoids demonstrate strong antioxidative activity. Direct mechanisms of antioxidative activity of flavonoids consist mainly in the scavenging of free radicals and reactive

oxygen species as well as in reducing their cellular production by inhibiting the activity of enzymes taking part in radical formation (xanthine oxidase, membrane-bound NAD(P)H oxidase, myeloperoxidase).

Their ability to chelate copper and iron ions prevents intracellular formation of reactive hydroxyl radicals [53].

Flavonoids also inhibit the activity of pro-inflammatory enzymes (phospholipase A2, cyclooxygenase, lipooxygenase) involved in the synthesis of inflammation mediators: prostaglandins and leukotrienes [54]; consequently, they contribute to the reduction in capillary and inflammatory reaction [55].

Anthraquinones

are common natural derivatives of anthracene (a polycyclic aromatic hydrocarbon with three fused benzene rings with various substituents). Their laxative properties have been made use of since ancient times [56]. Currently, they are also known to have antioxidative properties consisting in free radical scavenging [57].

REVIEW OF PRECLINICAL AND CLINICAL STUDIES WITH SINUPRET AND SINUPRET EXTRACT

As shown in *in vitro* studies, Sinupret improved the secretory activity of mucosal membranes which is of particular importance in inflammatory conditions. Disturbance of the transmembrane transport of chloride ions is considered to be one of the reasons behind the production of thick mucus in inflammatory conditions. This is due to the impaired function of the chloride channel known as cystic fibrosis transmembrane conductance regulator (CFTR). Disturbed activity of CFTR leads to increased density and accumulation of mucus followed by bacterial growth [58]. Natural flavonoids are capable of activating CFTR [59]. This was also demonstrated in mouse nasal cavity epithelial cell cultures as well as in murine in vivo models by means of the measurements of electric conductivity of nasal mucosa. A statistically significant and dose-dependent increase in the quantity of secreted chloride ions was demonstrated [59]. Similar premises were used by researchers who examined the impact of *Sinupret extract* on the quality of human bronchial epithelium, the difference consisting in that the quality of epithelium was also assessed in a tissue culture by measuring the frequency of movements of ciliated columnar epithelium within the bronchi following administration of the drug onto the epithelial surface or onto the basal membrane layer. The researchers observed increased secretion and an increased frequency of ciliary movements in the first case while no effects of this type were observed in the latter case. However, authors believe that mechanisms for the transport of the drug to the apical layer and thus for exerting the expected effect are possible *in vivo* [60].

Antibacterial activity comparable to that of isoniazide was demonstrated against *Mycobacterium tuberculosis* strains in human cell lines [24]. A similarly beneficial effect was observed for *Sinupret extract* with regard to inhibition of the growth of *Streptococcus pneumoniae* cultures inoculated onto mouse mucosal membranes as compared to a placebo control group; also the histopathological features of acute inflammation were less pronounced [61].

In experimentally-induced murine pleuritis, dose-dependent and significant reduction in the quantity of pleural effusion was observed in the study group receiving *Sinupret extract*. The effusion had lower leukocyte counts as well as lower PGE_2 and COX-2 levels within the lung tissues as compared to the control group [62].

Significant inhibition of proliferation of human respiratory viruses (influenza A, Chile 1/83 (H1N1), swine influenza California 07/2009 (H1N1), parainfluenza type 3, RSV, rhinovirus B subtype 14 (HRV 14), Coxsackie virus subtype A9 (CA9), adenovirus C subtype 5 (Adeno 5)) was demonstrated in tissue cultures exposed to *Sinupret extract* [63, 64]. Similar inhibition was also demonstrated in relation to strains resistant to certain antiviral drugs [64].

A randomized, controlled study in humans revealed that Sinupret extract used in supportive treatment of acute rhinosinusitis led to complete resolution of symptoms after 2 weeks of treatment in 60% of patients as compared to 25% of subjects in the placebo group [65].

A very well-designed and conducted multicenter, randomized, placebo controlled clinical study in a large population of 386 patients diagnosed with acute viral rhinosinusitis gave rise to a number of important findings with regard to the impact of *Sinupret extract* on the course of the disease [66]. Patients were assessed on five consecutive visits, with the number of symptom-free patients at visit 5 (day 14) according to the major symptoms score (MSS) assessment comprising the primary endpoint. Secondary endpoints consisted in results of SNOT-20 questionnaire self-assessments performed at each treatment visits, percentage of study discontinuations due to initiation of antibiotic treatment, percentage of patients with symptoms of active rhinosinusitis as assessed by means of an ultrasound scan at the completion of treatment an dur-

ing the 40-day follow-up period. The percentage of patients cured of rhinosinusitis as evidenced by ultrasound imaging at visit 5 was 73.2% in the *Sinupret extract* and 61.6% in the placebo group (p=0.0131). The MSS was 48.4% vs. 35.8% for the Sinupret extract group as compared to the placebo group (p=0,.063) with no significant difference in MSS values at baseline (p=0.4244). Mean difference in MSS scores at the completion of treatment was 0.86 (p=0.0117). The percentage of patients not experiencing improvement as the result of the treatment (final MSS > 50% of baseline value) was 14.7% vs 24.2%, respectively (p=0.0099). Quality of live assessments carried out by means of the SNOT-20 questionnaire revealed gradual decrease in the scores in the study group as well as in the control group, with significantly lower values recorded in the *Sinupret extract* group (p=0.0019).

SUMMARY

Abundant and well-documented data from reliable research articles are suggestive of plant extracts contained in *Sinupret extract* being biologically active as manifested by their anti-inflammatory, antiviral and antibacterial effect. Statistically significant and beneficial effect of Sinupret extract was also observed in clinical trials when the product was used in monotherapy of acute rhinosinusitis.

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