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ORIGINAL ARTICLE

Effects of *Pelargonium sidoides* extract on chemokine levels in nasal secretions of patients with non-purulent acute rhinosinusitis

Aleksandar Perić[a,b], Sandra Vezmar Kovačević[c], Aleksandra Barać[d], Dejan Gaćeša[e], Aneta V. Perić[f] and Danilo Vojvodić[g]

[a]Department of Otorhinolaryngology, Military Medical Academy Faculty of Medicine, University of Defense, Belgrade, Serbia; [b]Medigroup General Hospital, Belgrade, Serbia; [c]Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University in Belgrade, Belgrade, Serbia; [d]Clinical Center of Serbia, School of Medicine, University in Belgrade, Belgrade, Serbia; [e]ENT Hospital "Dr. Zutic", Belgrade, Serbia; [f]Institute for Pharmacy, Military Medical Academy Faculty of Medicine, University of Defense, Belgrade, Serbia; [g]Institute for Medical Research, Division of Clinical and Experimental Immunology, Military Medical Academy Faculty of Medicine, University of Defense, Belgrade, Serbia

ABSTRACT

Objective: Previous investigations suggest the use of extract from the roots of *Pelargonium sidoides* (EPs 7630) for improvement of the symptoms of uncomplicated upper airway inflammations, due to its antimicrobial and immunomodulatory actions. The aim of this investigation was to evaluate the effects of EPs 7630 on chemokine production in nasal mucosa and clinical parameters of patients with acute postviral rhinosinusitis (APRS).

Methods: Twenty-six ($n = 26$) APRS patients and 25 ($n = 25$) control subjects were included in this prospective study. We measured the concentrations of thirteen chemokines in nasal secretions of APRS patients and controls by flow cytometry. The patients with APRS were treated by EPs 7630 20 mg oral tablets, three times daily for 10 days. We compared the chemokine levels in nasal secretions, nasal symptoms and endoscopic findings in patients, before and after therapy.

Results: We found higher Total Symptom Score (TSS) and higher concentrations of MCP-1, MIP-1α, MIP-1β, MIP-3α, ENA-78 and IL-8 in nasal secretions of APRS patients than in controls. After therapy by EPs 7630, we found significant improvement in all symptoms and endoscopic findings of APRS. The concentrations of MCP-1, IP-10 and MIP-1β were significantly increased and levels of MIP-1α, ENA-78, GROα and IL-8 significantly decreased in nasal fluid samples after therapy. No adverse effects were reported during the treatment.

Conclusion: Our results suggest the presence of modulatory effects of EPs 7630 on production of chemokines regulating the function of neutrophils and monocytes in the site of inflammation of the nasal mucosa in patients with APRS.

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Cytokines; inflammation; nasal mucosa; plants; medicinal; rhinitis; sinusitis

Introduction

Acute rhinosinusitis (ARS) can be defined as an inflammation of the nasal and sinuses mucosa with less than 12 weeks in duration. About 98–99.5% of the cases of ARS are caused by viruses, especially rhinoviruses, coronaviruses, influenza and parainfluenza viruses, and adenoviruses[1–3]. This viral upper-airway infection, also known as common cold, usually passes for ten days with or without symptomatic therapy. However, in some cases, it can be followed by acute postviral rhinosinusitis (APRS), with prolonged duration of nasal complaints, not expecting the disease recovery and requiring the use of medications[2,3]. Secondary bacterial infection is observed in only 0.5–2% of ARS cases[2–4].

The role of inflammatory mediators in ARS is not explored in detail. Acute viral infections of the nasal mucosa stimulate the production and release of a variety of cytokines and chemokines in the respiratory epithelial cells[2–4]. The pathophysiology of APRS remains unclear. In this clinical entity, viral infection of the nose and sinus mucous membrane induces multiple changes, which include infiltration and activation of various inflammatory cells, especially neutrophils and monocytes and defects in the host and adaptive immune defence functions, as well as increase the risk of bacterial superinfection[3].

Traditionally, herbal medicines have been used for centuries for therapy of acute upper airway infections. Herbal preparation from the roots of *Pelargonium sidoides* was used for generations in South Africa for treatment of respiratory and gastrointestinal infections, due to its antiviral and antibacterial actions[5]. More than seven decades later, this polyphenol-rich extract was finally developed in Germany with

CONTACT Aleksandar Perić aleksandarperic1971@gmail.com Department of Otorhinolaryngology, Military Medical Academy Faculty of Medicine, University of Defense, Crnotravska 17, Belgrade, 11040, Serbia

coding name EPs 7630[6,7,i]. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 and International Consensus treatment on Allergy & Rhinology: Rhinosinusitis, the use of EPs 7630 is recommended as an option in therapy of ARS[3,8]. The immunomodulatory effects of this herbal drug are mediated mainly by stimulation of tumor necrosis factor alpha (TNF-α), interferon beta (IFN-β), IFN-γ and interleukin-10 (IL-10) production and reducing production of IL-6 and IL-15 in human respiratory tract epithelial cells[5–7,9,10]. Intensity of inflammatory reaction during the ARS depends on attraction of inflammatory cells. Chemokines are small cytokines that attract different inflammatory cells to the site of inflammation. However, *in vivo* studies related to the effects of EPs 7630 on chemokine production in nasal mucosa of patients with ARS were not previously conducted. This study was designed to compare the chemokine production in nasal mucosa of participants with and without APRS and to assess the effects of EPs 7630 on chemokine release in nasal secretions of patients with this uncomplicated form of ARS.

Patients and methods

Study design

This observational, prospective, case–control study was conducted from March 2018 to December 2019. The Ethics Committee of the Military Medical Academy, Belgrade, Serbia approved the study protocol (Approval No. 05/2019) and it was conducted according to the guidelines of the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Written informed consent was obtained from each participant. The STROBE reporting method has been followed.

Study participants

Twenty-six ($n = 26$) adult patients with mild-to-moderate APRS were enrolled in this investigation. Diagnosis of APRS was made according to the criteria presented in the EPOS 2012[2]. The patients had diagnosis of APRS if: (i) their complaints (obstruction/congestion of the nasal cavity, anterior nasal secretion, postnasal discharge, facial pain with the sense of pressure, and/or impaired sense of smell) were increased after 5 days or (ii) their symptoms were persistent after 10 days with less than 12 weeks duration. On nasal endoscopy, patients had edematous mucosa and increased non-purulent secretion especially from the middle meatus.

Twenty-five ($n = 25$) participants without any history of inflammatory disorders of nasal/paranasal sinus mucosa, selected for surgery of nasal septum and turbinate were enrolled for the control group.

Exclusion criteria: younger than 18 years and older than 65 years, chronic rhinosinusitis (CRS) with or without nasal polyps, surgery of the nose and paranasal sinuses within 6 months before the start of the study, systemic diseases that affect the nasal cavity and sinuses (eosinophilic and non-eosinophilic granulomatosis with polyangiitis, etc.), seasonal allergic rhinitis following pollen exposure, non-steroid anti-inflammatory drug-exacerbated respiratory disease, asthma, sensitivity to extract of *Pelargonium sidoides*, the use of anticoagulants and salicylates, therapy by antibiotics, corticosteroids and antihistamines within 4 weeks before the investigation, treatment by decongestants, mucolytics and hypertonic seawater within 7 days before the study, pregnancy, lactation, active cigarette smoking. Also, symptoms and signs of severe acute bacterial rhinosinusitis (fever $>$ 38 °C, persistent strong unilateral facial or tooth pain, profuse unilateral mucopurulent secretion and worsening of symptoms after initial improvement) were criteria for exclusion.

Treatment

The patients with APRS received herbal drug EPs 7630 oral tablets 3×20 mg/day (Umckalor[ii]), 10 days in total. Both the investigators and the patients were aware of the drug being given. The patients did not use other medications simultaneously with herbal drug.

Detection of chemokines

Nasal fluid samples were obtained from all 51 subjects, i.e. 26 with APRS, at the beginning of the study (Day 0, Visit 1) and again at day 10 (Visit 2) after the start of therapy by herbal medication, as well as from 25 control subjects, by absorption technique. Following cotton wool stick (Torlak, Belgrade, Serbia) insertion into the middle meatus during the 5 min, the stick watered with nasal fluid was put in an Eppendorf tube, containing 1 ml of transfer medium, as described in a previous study[11]. After the 30 min of inflammatory mediator diffusion into the medium and centrifugation of samples for 10 min and cell separation, the supernatants were frozen at −70 °C, until chemokine detection. The measurement of 13 chemokines, MCP-1, RANTES, IP-10, eotaxin, TARC, MIP-1α, MIP-1β, MIG, MIP-3α, ENA-78, GROα, I-TAC and IL-8 in nasal secretions of APRS patients and controls were done on a flow cytometer (NAVIOS, Beckmann Coulter, Brea, CA, USA), using bead-based multiple mediator detection commercial kit (LEGEND plex[iii]). The levels of chemokines were expressed in picograms/mililitres (pg/ml). The sensitivities of detection, assay range and coefficients of variation for biochemical parameters are presented in Table 1.

Clinical evaluation

The primary efficacy endpoints were the changes in the Total Symptom Score (TSS), the sum of intensities of 5 rhinosinusitis symptoms (nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, loss of the sense of smell) and the changes in the Total Endoscopic Score (TES), the sum of intensities of two endoscopic findings (mucosal edema, middle meatus mucopurulent secretion) at the Visit 1 and Visit 2. The secondary efficacy endpoints were the changes in individual scores for each nasal symptom and endoscopic finding.

Table 1. Sensitivity of detection, assay range and coefficient of variation for investigated mediators.

Mediator	Sensitivity of detection (pg/mL)	Assay range (pg/mL)	Coefficient of variation (%)
MCP-1	0.9	159.8–3488.4	6
RANTES	4.3	188.2–19563.0	5
IP-10	1.1	37.3–636.9	5
Eotaxin	1.4	ND–378.6	7
TARC	0.8	20.4–151.3	4
MIP-1α	2.1	7.0–1999.7	4
MIP-1β	1.4	6.1–195.4	4
MIG	9.4	ND–420.8	9
MIP-3α	2.5	6.7–155.2	4
ENA-78	1.1	12.5–935.4	7
GROα	6.7	ND–1550.9	3
I-TAC	1.1	8.1–139.1	6
IL-8	1.4	11.5–7636.4	8

Abbreviation. ND, non-detectable.

The nasal symptoms were assessed at the Visits 1 and 2 by the same rhinologist, using a visual analogue scale (VAS) (0–10 cm; 0 = absent, 10 = maximum intensity). Subjects that indicated symptoms to be from 0 to 3 were diagnosed as "patients with mild ARS", from 4 to 7 were diagnosed as "moderate ARS", while the patients with symptom severity from 8 to 10 with fever of above 38 °C for at least 3 days were diagnosed as "severe ARS". Only patients with mild and moderate ARS were included. During the investigation, patients recorded their symptom scores and noted the use of medications on diary cards and the investigator recorded scores at the Visit 2. The investigator evaluated compliance of the treatment by insight into the diary cards. Also, TSS in control subjects was assessed. At Visits 1 and 2, an experienced rhinologist evaluated the presence of mucosal edema and secretion in the middle meatus by use of nasal endoscopy (4 mm 0° endoscope, Karl Storz – Endoscope SE & Co, Tuttlingen, Germany). Four-point scales were used for assessment of endoscopic findings, according to the Pfaar et al.[12]. Mucosal edema scored from 0 (no edema) to 3 (severe edema); middle meatus secretion from 0 (none) to 3 (profuse). The maximum TES was 12, bilaterally. According to the EPOS 2012[2], radiological examinations (X-ray, CT, MRI) were not used in the diagnostics of APRS.

Safety

The potential mild, moderate and severe adverse effects were recorded during the study. The laboratory testing and assessment of vital signs were performed at the Visit 2. All patients were aware of potential adverse events of herbal drug. Also, the development of any complications of ARS (orbital, bony, endocranial) was recorded during this investigation.

Strength of the study and statistical analysis

The results of study conducted by De Corso et al.[13] demonstrated the highest difference in the concentrations of chemokine eotaxin in nasal fluid in patients with rhinosinusitis in comparison to subjects with healthy nasal mucosa (128.9 ± 51.7 pg/ml *versus* 16.4 ± 10.7 pg/ml, $p < .001$). We have the criterium that the expected strength of the effect was 0.4 (between-group difference of more than 30%). The power analysis (G*Power 3.1.9 programme, Heinrich Heine Univerität, Düsseldorf, Germany) predicted that simple sizes of 16 participants in each group would be required to reach the study power of 80%. The type I error (α level) was set to 0.05. The parameters were presented as mean ± standard deviation. For between-group comparison, we used the non-parametric Mann–Whitney *U* test. For paired comparisons in a group, a Wilcoxon's test was used. *p* values <.05 were considered significant. The analysis was done by using the Statistical Package for the Social Sciences, version 15.0 software (SPSS Inc., Chicago, IL, USA).

Table 2. Baseline demographic, clinical and biochemical data.

Parameter	APRS ($n = 26$)	Controls ($n = 25$)	*p* Value
Male/female ratio	15/11	15/10	.904
Age (years)[a]	39.7 ± 12.4	40.8 ± 11.9	.842
Total Symptom Score[a]	33.2 ± 2.3	12.5 ± 2.2	<.001
Total Endoscopic Score[a]	9.7 ± 1.3	0	/
MCP-1[a]	465.3 ± 314.1	267.9 ± 92.6	.003
RANTES[a]	938.9 ± 1107.7	624.4 ± 482.7	.749
IP-10[a]	199.8 ± 155.4	128.2 ± 79.9	.181
Eotaxin[a]	23.1 ± 37.8	12.5 ± 12.2	.510
TARC[a]	10.9 ± 17.4	7.8 ± 14.6	.472
MIP-1α[a]	703.6 ± 265.6	333.5 ± 164.3	<.001
MIP-1β[a]	62.9 ± 31.4	22.2 ± 14.5	<.001
MIG[a]	0.5 ± 1.5	1.0 ± 3.4	.893
MIP-3α[a]	56.6 ± 29.1	24.4 ± 14.4	<.001
ENA-78[a]	335.6 ± 150.8	74.5 ± 62.5	<.001
GROα[a]	153.1 ± 243.3	144.2 ± 167.8	.934
I-TAC[a]	20.3 ± 33.4	11.3 ± 20.1	.433
IL-8[a]	589.8 ± 518.7	216.7 ± 225.1	<.001

[a]Values are presented as mean ± standard deviation (SD). The concentrations of inflammatory mediators are expressed in pg/mL.

Results

The baseline demographic, clinical and biochemical data are presented in Table 2.

We found significantly higher TSS ($p < .001$), as well as higher concentrations of MCP-1 ($p = .003$), MIP-1α ($p < .001$), MIP-1β ($p < .001$), MIP-3α ($p < .001$), ENA-78 ($p < .001$) and IL-8 ($p < .001$) in patients with APRS than in control subjects (Table 2, Figure 1).

After the treatment with EPs 7630, we found significant improvement in all symptoms and endoscopic findings ($p < .001$ for all parameters) in patients with APRS (Table 3). However, we found better effects in the improvement of loss of the sense of smell (68.9%), facial pain/pressure (67.2%) and nasal obstruction (66.5%) and worse effects in the

improvement in postnasal drip (55.5%) and rhinorrhea (52.9%) score. The main relative improvement in TSS was 62.4% (Table 3). Regarding the endoscopic findings, we found the decreased mucopurulent secretions for 65.5% and mucosal edema for 63.8%. The main relative improvement in TES was 64.5% (Table 3).

The post-treatment concentrations in nasal secretions were significantly increased for MCP-1 (45.5%), IP-10 (81.4%) and MIP-1β (26.9%) ($p = .001$; $p < .001$; $p = .025$, respectively) and significantly decreased for MIP-1α (42.3%), ENA-78 (53.9%), GROα (20.3%) and IL-8 (49.4%) ($p < .001$; $p < .001$; $p = .005$; $p < .001$, respectively) (Table 4, Figure 2).

No adverse events were noted during the therapy by EPs 7630.

Discussion

Inflammatory mediator-related investigations in patients with ARS have rarely been performed and our study is the first one which evaluated the chemokine production by nasal mucosa during the therapy with *Pelargonium sidoides* extract. According to previous investigations, contents of nasal secretions reflect the inflammatory status of the nasal mucosa and evolution of mucosal disease[14–16]. Nasal epithelial cells elicit their own repertoire of immune responses and actively prevent pathogens from damaging the airway. Upon viral infection, nasal epithelium releases not only anti-microbial surfactants and mucus to delay pathogen transmission in the airway, but also produces various cytokines and chemokines to drive immune responses against invading pathogens in the airways[3]. Viral infection of epithelial cells leads to an increased production of cytokines (IFN-β, IFN-γ, IL-1β, TNF-α and IL-6) and chemokines (IL-8, IP-10, I-TAC, etc.)[3,14–23]. Our results showed increased nasal secretion levels of chemokines related to neutrophil attraction and activation (IL-8, ENA-78) and nonselective chemokines (MCP-1, MIP-1α, MIP-1β, MIP-3α), those that attract different inflammatory cells (eosinophils, neutrophils, monocytes) to the site of inflammation in APRS patients than in controls. These results suggest that in APRS, the increased syntheses of these chemokines may relate to the prominent tissue neutrophilia, which can prepare the nasal and sinus mucosa for defence against possible bacterial superinfection.

Herbal drug EPs 7630 showed many actions against viral and bacterial infections. It increases ciliary beat frequency (CBF) of an adherent monolayer culture of human nasal epithelial cells[6]. This drug demonstrates effects against influenza and parainfluenza virus, respiratory syncytial virus, and, especially, human coronavirus by herbal bioflavonoids and

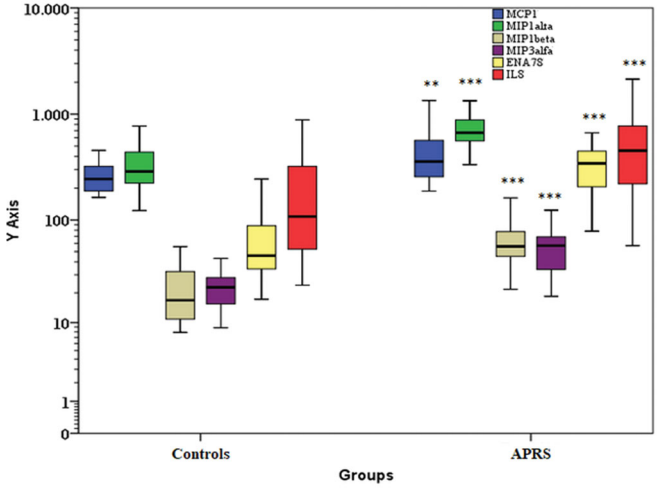

Figure 1. Comparison of chemokine levels in nasal secretions between control participants (Controls) and APRS patients. Only chemokine levels with statistically significant differences are presented. Due to the high variations in chemokine concentrations, they are presented as logarithmic values. Values of statistical significance: $*p < .05$; $**p < .01$; $***p < .001$ *versus* corresponding chemokine levels from control group.

Table 4. Biochemical data before and after therapy by herbal medicine, as well as relative changes of investigated mediators.

Parameter	Before therapy (V1) (Mean ± SD)	After therapy (V2) (Mean ± SD)	*p* value	Relative changes[a] (Mean ± SD)
MCP-1	465.3 ± 314.1	598.3 ± 327.3	.001	45.5 ± 54.8
RANTES	938.9 ± 1107.7	902.8 ± 1038.9	.485	−4.7 ± 38.1
IP-10	199.8 ± 155.4	307.6 ± 179.4	<.001	81.4 ± 80.5
Eotaxin	23.1 ± 37.8	26.5 ± 50.0	.551	21.1 ± 90.7
TARC	10.9 ± 17.4	10.8 ± 19.5	.937	−17.3 ± 38.9
MIP-1α	703.6 ± 265.6	375.5 ± 166.8	<.001	−42.3 ± 26.0
MIP-1β	62.9 ± 31.4	73.0 ± 32.0	.025	26.9 ± 49.0
MIG	0.5 ± 1.5	0.6 ± 1.7	.917	−11.5 ± 32.6
MIP-3α	56.6 ± 29.1	55.8 ± 26.9	.603	7.7 ± 43.3
ENA-78	335.6 ± 150.8	142.4 ± 98.8	<.001	−53.9 ± 25.4
GROα	153.1 ± 243.3	62.1 ± 114.4	.005	−20.3 ± 29.8
I-TAC	20.3 ± 33.4	17.4 ± 32.0	.583	−10.0 ± 41.2
IL-8	589.8 ± 518.7	224.5 ± 157.6	<.001	−49.4 ± 34.0

The concentrations of inflammatory mediators are expressed in pg/mL.
[a]The relative changes of investigated parameters: (value – baseline value)/baseline value.
Abbreviations. SD, standard deviation; V1, visit 1 (before treatment); V2, visit 2 (after treatment).

Table 3. Clinical data before and after therapy by herbal medicine, as well as relative changes of investigated parameters.

Parameter	Before therapy (V1) (Mean ± SD)	After therapy (V2) (Mean ± SD)	*p* Value	Relative changes[a] (Mean ± SD)
Nasal obstruction	6.5 ± 0.6	2.2 ± 0.4	<.001	−66.5 ± 7.6
Rhinorrhea	6.5 ± 0.4	3.0 ± 0.8	<.001	−52.9 ± 14.4
Postnasal drip	6.4 ± 0.5	2.8 ± 0.6	<.001	−55.5 ± 9.5
Facial pain/pressure	6.6 ± 0.6	2.1 ± 0.3	<.001	−67.2 ± 6.0
Loss of the sense of smell	6.5 ± 0.5	2.0 ± 0.5	<.001	−68.9 ± 7.8
Total symptom score	33.2 ± 2.3	12.1 ± 1.1	<.001	−62.4 ± 4.0
Mucosal edema	5.8 ± 0.4	2.2 ± 0.4	<.001	−63.8 ± 6.2
Mucopurulent secretions	5.1 ± 0.7	1.7 ± 0.6	<.001	−65.5 ± 10.8
Total endoscopc score	10.7 ± 1.3	4.1 ± 0.8	<.001	−64.5 ± 5.8

[a]The relative changes of investigated parameters: (value – baseline value)/baseline value.
Abbreviations. SD, standard deviation; V1, visit 1 (before treatment); V2, visit 2 (after treatment).

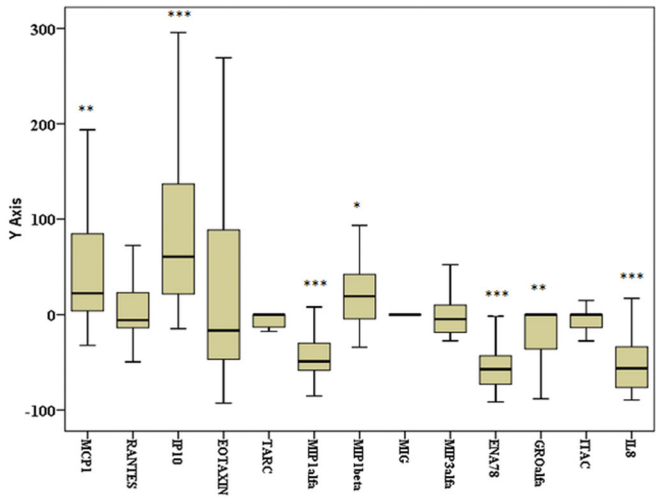

Figure 2. Logarithmic values of the relative changes of investigated chemokines. Chemokine levels above the zero (0) line (MCP-1, IP-10, MIP-1β) are increased and those below the zero (0) line (MIP-1α, ENA-78, GROα, IL-8) are decreased after therapy by EPs 7630. The statistical significances in changes of chemokine levels: $*p < .05$; $**p < .01$; $***p < .001$.

polyphenol-induced inhibition of enzyme neuraminidase, very important in viral replication[6]. EPs 7630 had direct effect against a spectrum of Gram-positive and Gram-negative bacteria by stimulating nonspecific immune response[9]. This mode of actions includes inhibition of bacterial adhesion to epithelial cells, stimulation of phagocytosis, nitric oxide (NO) release, and oxidative burst[6,9]. However, immunomodulatory actions of this drug are also very interesting. A large body of evidence indicates that induction of nonspecific host defence mechanisms against a number of pathogens, especially viruses, is related to the IFN-β and IFN-γ[6,9]. Previous *in vitro* investigations demonstrated an up-regulation of these cytokines, as well as TNF-α after the stimulation of human macrophages, lymphocytes and epithelial cells with *Pelargonium sidoides* extract[6,9].

Our results suggest that therapy of APRS patients by EPs 7630 stimulates MCP-1, IP-10 and MIP-1β and inhibits MIP-1α, ENA-78, GROα and IL-8 production in the nasal and sinus mucosa. MCP-1 is secreted by monocytes and macrophages and this chemokine exhibits chemotactic activity for monocytes, basophils and eosinophils, but it does not attract neutrophils[17]. IP-10 is secreted by several cell types (monocytes, endothelial cells and fibroblasts) in response to IFN-γ action. This mediator has been attributed to several roles, such as chemoattraction for monocytes, macrophages, T-cells and natural killer cells, all very important in defence against pathogens[17]. Both MCP-1 and IP-10 have functions mostly connected to monocyte actions[17]. On the other hand, ENA-78, GROα and IL-8 are chemokines related to function of neutrophils and they are produced by nasal epithelial cells, monocytes and macrophages following stimulation of these cells with pro-inflammatory cytokines IL-1β and TNFα. All these chemokines stimulate the chemotaxis of neutrophils to the site of inflammation caused by viral and bacterial infection[18]. Although neutrophils have protective functions against bacterial and viral infections, a recent *in vitro* study, conducted by Kao et al.[19] demonstrated that serine proteases, enzymes derived from neutrophils showed detrimental effects on the mucosal barrier integrity with increased permeability, allowing for potential bacterial infection. Accordingly, we speculate that reduction of neutrophil chemokines by *Pelargonium sidoides* leads to lower production of neutrophil proteases, resulting in better protection and stabilization of respiratory epithelium in the nasal mucosa. There is a difficult-to-explain phenomenon that nasal secretion concentration of MIP-1α was decreased and MIP-1β was increased after the therapy by herbal drug. MIP-1α and MIP-1β are distinct but highly related proteins that shared 68% identical amino acids. Primary sources of these proteins are monocytes and macrophages. According to previous investigations, it seems that differences in other 32% of the polypeptide chain do not determine important differences in biological activity between these two proteins[20].

In our study, the patients reported no adverse effects. However, previous studies reported allergic reactions, hemorrhage and liver toxicity following therapy with extract of *Pelargonium sidoides*[21,22]. Therefore, a theoretical risk of interactions between active substances of this herbal medicine and anticoagulants such (e.g. warfarin), and antiplatelet drugs (e.g. aspirin) was notified. There are also cautions against use of the tested substance during pregnancy and lactation and in patients with serious liver diseases[21,22]. Regarding the duration of EPs 7630 administration in patients with common cold, previous studies showed that both pediatric and adult patients should receive treatment for a maximum of 7–10 days[5,22,23]. Due to the presence of more intensive and refractory symptoms in patients with APRS and the possibility of the presence of side effects of *Pelargonium sidoides*, we decided to administrate this herbal drug for 10 days.

This study has some limitations, as it was conducted in a single university hospital. It was not a placebo-controlled investigation, as we did not obtain the approval from our Ethics Committee to conduct such study. Therefore, due to our financial limitations, we performed only biochemical analysis of chemokine profile in nasal fluid, but not a Polymerase Chain Reaction (PCR) analysis of nasal and sinus mucosa regarding the capacity for the production of these chemokines.

Conclusion

According to our results, *Pelargonium sidoides* extract acts as a modulator of upper respiratory tract-associated immunological responses by increasing production of monocyte-related and decreasing production of neutrophil-related chemokines. These effects could modulate inflammatory responses, as well as activation and migration of monocytes and neutrophils to the site of acute inflammation. By modulation of inflammation, this herbal drug significantly improves symptoms and endoscopic findings in patients with APRS.

Notes

i. EPs 7630 is a registered trademark of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.
ii. Umckalor is a registered trademark of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.
iii. LEGEND plex is a trademark of Bio Legend, San Diego, CA, USA.

Transparency

Declaration of funding

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Declaration of financial/other relationships

The authors have no conflict of interest to declare. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Conception and design: A.P., S.V.K., D.V.

Analysis and interpretation of the data: A.P., S.V.K., A.B., D.G., D.V.

Drafting of the work and critical revision for important intellectual content: A.P., S.V.K., A.B., D.G., A.V.P., D.V.

Final approval of the version to be published: A.P., S.V.K., A.B., D.G., A.V.P., D.V.

All authors agree to be accountable for all aspects of the work.

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Data availability statement

The data that support the findings of this study are not publicly available. Data are, however, available from the authors upon reasonable request.

ORCID

Aleksandar Perić http://orcid.org/0000-0002-8453-7272

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