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Siberian Fir Extract Used in Complex Therapy of Acute Respiratory Viral Infections

Valery Petrovich Sergun[1], Evgenia Bereslavets[2], Valentina Nikolaevna Burkova[3], Valeriy Mikhailovich Poznyakovsky[4], Elena Ragozinnikova[5], Boisjoni Tokhiriyon[4*]

[1,3]Research and Production Association «Biolit», Tomsk, Russia.
[2]Department of Technological Entrepreneurship, Kuzbass State Agricultural Academy, Kemerovo, Russia.
[4]Scientific and Educational Center for Applied Biotechnology and Nutrition, Kemerovo State Medical University, Kemerovo, Russia.
[5,6*]Department of Management, Entrepreneurship and Engineering, Ural State University of Economics, Ekaterinburg, Russia.

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ABSTRACT
A new dietary supplement based on Siberian fir extract has been developed. The novelty of the product has been patented. The essence of the technology lies in the concentration of the extract under vacuum at a gentle temperature (40-50°C), which ensures maximum extraction of biologically active substances and stability of their functional properties. The dietary supplement was identified by the determination of α-bisabolol, borneol and α-terpineol alcohols, bornyl acetate and ketone esters. Phenolic compounds and maltol with antioxidant properties were identified. Evidence-based medical studies were conducted on the efficacy of the developed product by including it in the diet of patients with acute respiratory diseases. Clinical studies on the effectiveness of the product were conducted on a group of patients with acute respiratory viral infections (ARVI). The patients received the dietary supplement in addition to the basic therapy, three tablespoons every 4 hours until the symptoms were alleviated, then one tablespoon four times a day, 30 minutes before meals, dissolved in ¼ glass of water. The total duration of treatment was 10 days (for the main group). The comparison group consisted of 30 patients with similar manifestations of ARVI, who were prescribed only basic therapy in accordance with the current clinical recommendations of the Ministry of Health of the Russian Federation. The patient groups were compared by age (18-60 years), gender and concomitant disease. The duration of the main clinical symptoms in patients with ARVI and their proportion as well as serum interferon levels were analysed. The results of the studies showed the efficacy and safety of the tested form of the dietary supplement and its therapeutic potential in the complex therapy of patients with ARVI.

Keywords: Siberian Fir Extract, Dietary Supplement, Identification of Active Principles, Complex Therapy of Acute Respiratory Viral Infections, Efficacy.

1. INTRODUCTION

Preventing and addressing acute respiratory viral infections (including nasopharyngitis, tracheobronchitis, tonsillitis, influenza, COVID, etc.) is a priority due to their prevalence, negative effects on health and overall quality of life. One example is the symptoms of post-COVID, which are often recorded after the disease. An effective way of correcting metabolic disorders is the use of biologically active natural compounds and their complexes as part of basic therapy. The leader in its content is the coniferous, with the Siberian fir (A. Sibirica) taking a special place [1-7].

Objects of Study

A process for obtaining an aqueous extract of Siberian fir, which is part of the water vapour distillate of the fir branches distilled together with the fir oil and called "Florentine water", has been patented. The extract is concentrated 10-fold under gentle conditions (40-50 degrees Celsius) in a vacuum, which ensures the most complete extraction of the biologically active substances, their stability and functional properties. The product is registered by the Ministry of Health of the Russian Federation as a dietary supplement, is a liquid of pink to light orange colour with a pleasant taste and smell of pine needles.

According to the available information [8-11], pine extract is an adaptogen, that is, it increases the body's resistance to unfavourable conditions. It has a stimulating effect on haematopoiesis, the immune system, regeneration processes, shows antimicrobial, anti-inflammatory, hepatoprotective effects, disinfects the

respiratory tract and the gastrointestinal tract, is not harmful to the body and has a positive effect on the immune system, regeneration processes, exhibits antimicrobial, anti-inflammatory, hepatoprotective effects, sanitizes the respiratory tract and gastrointestinal tract, it is non-toxic and has no allergenic, carcinogenic and embryotoxic properties. Thus, the water extract of Siberian fir needles is an affordable and safe natural adaptogen with a wide range of action.

Clinical studies have shown the effectiveness of the drug in the complex therapy of cardiovascular diseases, gastrointestinal tract diseases. In addition, the dietary supplement is successfully used for diseases of the lower and upper respiratory tract. The extract of Siberian fir needles increases the body resistance and is effective as a preventive measure for viral infections, colds, fatigue, vitamin deficiencies.

It is known that conifers contain phytoncides that have a detrimental effect on pathogenic microflora. Experiments on 6 strains of various microorganisms showed that Siberian fir extract significantly inhibits their growth and development. After a month of complex treatment, including taking fir extract, the immune system of patients significantly improves: the number of T-lymphocytes increases, the amount of immunoglobulin G is normalized, and the number of circulating immune complexes decreases. The duration of treatment is reduced by 1.4-1.6 times. Thus, the inclusion of Siberian fir extract in the treatment regimen for patients with acute respiratory viral infections has a positive effect on the course of the disease and reduces the duration of treatment [12-15].

Purpose of Study

The purpose of this study was to assess the effectiveness, tolerability and safety of a dietary supplement based on Siberian fir extract in comparison with basic therapy in adult patients with ARVI.

Clinical trials were conducted on a group of 30 patients with ARVI with various manifestations of the disease - runny nose, scratchy and / or sore throat, cough, fever, headache, arthralgia. Patients received the dietary supplement along with basic therapy, 3 tablespoons (50 ml) every 4 hours until symptoms were relieved, then 1 tablespoon 4 times a day, 30 minutes before meals, pre-dissolved in ¼ glass of water. The total course lasted 10 days (for the main group).

The comparison group of 30 patients with similar manifestations of ARVI, who were prescribed only basic therapy in accordance with the current clinical recommendations of the Ministry of Health of the Russian Federation.

The study groups of patients were compared by age (18-60 years), gender and concomitant pathology.

2. MATERIAL AND METHODS

Influenza viruses, adenoviruses, RS-rhinovirus, parainfluenza, bocavirus, metapneumovirus, herpes simplex virus-1,2, EBV and HHV-6 were determined by a nasopharyngeal/oropharyngeal smear by PCR. In case of itching and rashes on the mucous membranes and skin, a local PCR smear for herpes viruses was performed, as well as a nasopharyngeal smear for SARS-Cov-2 RNA. IFN status with analysis of spontaneous, serum, induced IFN-α, IFN-γ and the degree of IFN suppression were studied by the method introduced by Grigoryan S.S. in "Evaluation of the interferon status of human subjects by whole-blood specimens." The study of IFN-like activity of blood serum and supernatant of blood cell cultures incubated in a medium with the addition of phytohemagglutinin (PHA) or Newcastle disease virus (NDV), as well as without induction, was carried out according to the approved method. Statistical analysis includes data validation and analysis of the obtained variables. Statistical processing was carried out using methods of variation statistics with Microsoft Excel and STATISTICA-12.

The evaluation of the relative and absolute indicators included the percentage of data (%), the calculation of the arithmetic mean (M), the standard deviation (σ), the standard error of the mean (m), the maximum (Max) and minimum (Min) values.

Non-parametric statistical criteria were used to analyse the qualitative variables, and parametric or non-parametric statistical criteria were used for the quantitative variables after checking the distributions for conformity with the normality of the distribution.

Differences were considered reliable at $p < 0.05$, very reliable at $p < 0.01$ and $p < 0.001$, unreliable - $p > 0.05$.

The study involved 60 patients with ARVI aged 18-60 (48.7±11.4) years, of whom 34 (56.7%) were women and 26 (43.3%) were men (see Table 1). The analysed patient groups were comparable in terms of age, gender and comorbidities.

Table 1: Distribution of patients by gender and age.

Patient Groups	**Gender**				**Age**					
	Male		Female		18-30		31-45		46-60	
	n	%	n	%	n	%	n	%	n	%
Main	12	40	18	60	9	30	12	40	9	30

Control	14	46,7	16	53,3	7	23,3	13	43,4	10	33,3

The main complaints at the time of treatment were fever, weakness, sore throat, dry cough and headache. Concomitant illnesses were found in 18 people (60 %) in the main group and in 17 (56.7 %) in the control group (see Table 2).

Table 2. Clinical characteristics of patients with acute respiratory viral infections before therapy (visit 1).

№	Clinical Symptoms	Main group (1) n=30		Control group (2) n=30		Reliability P1-2
		n	%	n	%	>0,05
1	Weakness	27	90	29	96,7	>0,05
2	Headache	19	63,3	17	56,7	>0,05
3	Fever up to 38 Above 38	21 9	70 30	23 7	76,7 23,3	>0,05
4	Scratchy/sore throat	24	80	23	76,7	>0,05
5	Dry cough	25	83,3	26	86,7	>0,05
6	Shortness of breath	4	13,3	6	20	>0,05
7	Nausea, vomiting	3	10	2	6,7	>0,05
8	Abdominal pain	4	13,3	3	10	>0,05
9	Rhinitis	6	20,0	4	13,3	>0,05
10	Itching and rash (on mucous membranes/ skin)	4	13,3	5	16,7	>0,05
11	Comorbidities	18	60	17	56,7	>0,05

There were no statistically significant differences in age, gender, and initial clinical manifestations of the disease between the groups. The ethical and legal aspects of the clinical studies were observed and the latter were conducted in accordance with the protocol and principles of the Helsinki Declaration of the World Medical Association (Fortaleza, 2013), the rules of Good Clinical Practice (ICH GCP), the Constitution of the Russian Federation, Federal Law of the Russian Federation No. 323-FZ of November 21, 2011 "On the Fundamentals of Health Protection of Citizens in the Russian Federation", other relevant legislative acts and orders of the Ministry of Health of the Russian Federation. Prior to the study, approval was obtained from the local ethics committee of the research center.

The studies were carried out at the Central Research Institute of Epidemiology of Rospotrebnadzor of the Russian Federation under the supervision of the head of the clinical department of infectious pathology, doctor of medical sciences Ponezheva Zh.B.

3. RESULTS AND DISCUSSION

The chemical composition of the obtained extract was identified using gas chromatography and mass spectrometric detection. The most of the identified compounds are alcohols α-bisabolol, borneol and α-terpineol, ester bornyl acetate and ketones. Table 3 shows the content of the main biologically active substances in the obtained extract.

UV spectroscopy showed the presence of phenolic compounds with antioxidant properties in the studied object. Using high-performance liquid chromatography, maltol was identified in a fairly high amount, which is also an antioxidant and is widely used as a bactericidal and antimicrobial agent.

Table 3. Content of the main biologically active substances in the concentrate of Siberian fir aqueous extract.

Indicator	Sample content
Total polyphenols calculated as gallic acid, mg/100 g	20,0
Dihydroquercetin, mg/100 ml	8,5
Tannins calculated as tannin, mg/100 ml	13,5
Vitamin C, mg/l	10,0
Copper, mg/kg	4,1
Zinc, mg/kg	0,33
Iron, mg/kg	205,8
Manganese, mg/kg	0,83
Selenium, μg/l	28,0

The following pathogens were identified in the study groups by PCR: rhinovirus in 35%, adenovirus in 11.7% of the observed patients, parainfluenza type 1 and respiratory syncytial virus in 1 case each, mixed infection (rhinovirus in combination with Streptococcus pneumoniae and Staphylococcus aureus) was observed in 4 patients (6.7%), bacterial flora in 3 cases (Streptococcus pneumonia, Staphylococcus aureus, mycoplasma) and opportunistic flora in insignificant titers in 7 patients, herpesvirus infection in 11 patients (18.3%) (HSV-1,2 in 8, EBV-3), Covid-19 was detected in 2 patients, and the pathogenic agent could not be detected in 10 patients (Table 4).

Table 4. Pathogenic agents identified in patients by PCR.

Pathogen	**Number of patients (n=60)**	**%**
Rhinovirus	21	35
Adenovirus	7	11,7
Parainfluenza	1	1,7
RS virus	1	1,7
Mixed infection	4	6,7
Bacterial flora	3	5
EBV	3	5
HSV-1,2	8	13,2
Covid-19	2	3,3
Not verified	10	16,7

Based on the results of determining the degree of IFN system suppression in patients with ARVI (n=60), a moderate reaction of the IFN system was detected in 19 (31.7%) patients, a weak (insufficient) reaction of the defense system was detected in 32 (53.3%) patients, and depression of the IFN system was detected in 9 (15%) patients.

A comparative analysis of the therapy effectiveness in patients was assessed by the duration of the following symptoms: headache, fever, weakness, cough, nasal congestion/rhinorrhea, scratchy and sore throat (Table 5).

At the following visits, the patient brought a completed individual diary with an assessment of the severity of each symptom on a 3-point scale: 0 - no symptom, 1 - mild manifestation, 2 - moderate manifestation, 3 - severe manifestation of the symptom.

During observation and treatment, patients recorded drug tolerance and possible adverse effects of therapy. Thermometry was performed twice a day, and an objective examination was performed during visits.

Table 5. Duration of the main clinical symptoms in patients with ARVI (visit 2)

Study group	**Headache**	**Fever**	**Weakness**	**Cough**	**Rhinitis**	**Pharyngitis**
Main	3,1±0,3	3,7 ±0,4	3,9 ± 0,3	5,7 ±1,1	4,5±0,3	4,1 ± 0,2
Control	3,9±0,7	5,9±0,6	4,7±0,3	7,1+1,9	5,1±0,5	4,7±0,7

It was noted that the severity and duration of the temperature reaction were comparable in both groups before the start of therapy. Higher temperature was recorded for the main group for 3 days (1-4 days), for the control group for 5 days (2 to 6 days). No significant differences in the relief of symptoms were found, however, symptoms of intoxication and catarrhal symptoms in the main group tended to improve earlier. Thus, according to the diaries of patients in the main group, in the first three days of treatment, a decrease in temperature to 37.5 occurred in more than 75% of patients versus 43% in the control group. Normal temperature was already observed on the 4th day in 29 patients (96.7%) and only one patient with HSV-2 recorded a temperature above 37 in the evening on the 9th day (2nd visit). In the control group, according to the patients' diaries, the temperature normalized on the 4th day only in 26.7% of patients, and only on the 7th-9th day from the start of treatment normal temperature was recorded in 90% of cases (2 patients were hospitalized with pneumonia, 1 patient was diagnosed with Covid-19).

When comparing the need and frequency of treatment correction with the addition of antibacterial therapy in the study groups, it was noted that in the main group such correction was not required, in the control group - 3 patients received such a course and 2 patients were hospitalized on the 5th day due to the development of pneumonia. On the 3rd day, the proportion of patients with severe weakness in the main group significantly decreased by 56.7%, while in the control group 73.3% of patients complained of weakness ($p = 0.028$). On the 7th day of therapy, the proportion of patients without cough in the main group was 63.3% (19) which was significantly higher than in the comparison group - 36.7% (11) ($p < 0.02$).

A decrease in the severity and intensity of this symptom in the study groups was recorded for all patients on the

2nd visit (see Table 5) and was practically absent in patients on the 3rd visit (see Table 6). A pronounced tendency to shorten the catarrhal and intoxication period and accelerate the recovery of patients in the main group was revealed, which indicates the advisability of an in-depth study of the effectiveness and mechanisms of action of the drug [16-21].
At the same time, the tolerability of the dietary supplement was assessed as "very good" in 27 (90%) and "good" (10%) patients, side effects and serious adverse events were not recorded during the observation period.
As can be seen from Table 5, in the main group of patients receiving the dietary supplement, there were significantly fewer patients who still had clinical symptoms.

Table 6. The proportion of the main clinical symptoms in the study groups at Visit 3 (21±2 days).

№	Clinical symptoms	Main group (1) n=30		Control group (2) n=29		Reliability P
		n	%	n	%	
1	Weakness	2	6,7	5	17,2	<0,01
2	Headache	1	3,3	2	6,9	<0,05
3	High temperature (37,5 and higher)	1	3,3	2	6,9	<0,05
4	Scratchy/sore throat	2	6,7	5	17,2	<0,01
5	Cough	1	3,3	3	10,3	<0,001
6	Shortness of breath	-	-	1	3,4	-
8	Itching and rash (on mucous membranes/ skin)	1	3,3	2	6,9	-<0,05
9	Rhinitis	-	-	1	3,4	-

The patient with COPD in the main group scored the severity of residual symptoms (weakness, cough) 1, the patient with recurrent herpesvirus infection scored the weakness and headache 1, an increase in temperature to 37.5 in the evening, itching, rashes on the mucous membranes and skin of the right buttock were scored 2 [22-26]. Exacerbation was detected during examination at the 3rd visit, in connection with which adequate antiviral therapy was prescribed: Valtrex 1000 mg 2 times 5 days + Panavir locally 5 days + Populin 3 capsules 3 times a day for a month for an outbreak of recurrent genital HSV-2. In the control group, symptoms were detected in 5 people with a severity of 2 points, in 3 patients - cough, weakness, headache, weakness - of 1 point. In the main group, after completion of the course, a pronounced stabilization of the interferon status was noted after the course of treatment and the absence of virus excretion in all cases [27-34].
When studying the serum interferon indicators (IFN - alpha and gamma), statistically significant differences between the groups both before and after the treatment were not noted. In the study groups, before the start of therapy, IFN - alpha production was approximately two times lower than the conditional norm [35-40]. A tendency towards normalization of IFN indicators after treatment was shown. None of the groups demonstrated a reliable change in the IFN-alpha level established as a result of the therapeutic and preventive measures (Table 7)[40-45].

Table 7. The dynamics of serum interferon indicators in patients with ARVI.

IFN (pg/vk)	Healthy	Indicator dynamics for study groups					
		Main group			Control group		
		Before treatment (n=30)	After treatment (n=30)	P	Before treatment (n=30)	After treatment (n=29)	p
IFN-α	8,1±0,9	3,8±1,1*	4,6±0,9*	p>0,05	4,1±0,9*	4,7±1,4	p>0,05
IFN-γ	6,3±1,0	2,6±0,4*	4,7±0,7	p<0,05	3,3±1,0*	4,1±1,7	p>0,05
Note: quantitative characteristics are given as mean ± standard deviation (M±Se). Bold font indicates significant differences in groups before and after treatment according to Mann-Whitney criterion at p <0.05; *- significant differences in relation to the group of healthy people							

In both study groups, a significant decrease in INF-alpha and -gamma concentrations in the blood serum of patients with ARVI was observed compared to similar indicators in the group of healthy individuals. The greatest decrease in INF-a was observed in patients with herpesvirus infection. A significant increase in the level of IFN-γ in the blood serum after treatment was noted in the main group (4.7±0.7; p <0.05). In the control

group, a tendency towards positive dynamics of the analysed IFN and cytokine parameters was observed, but without reaching the target level.

The analysis of the interferon status (IFN status) after therapy showed a significant improvement in the IFN parameters analysed in the main group. A complete normalisation of the IFN status response was observed in 5 (16.7%) patients, the number of patients with a moderate response of the IFN system increased to 17 (56.7%), a weak (insufficient) response of the defence system was observed in 6 (20%) of the subjects. The number of patients with a depression of the IFN system decreased twofold from 13.3% to 6.7 (2 patients). In the control group, a significant improvement in IFN status was observed only in 13 (43.3%) patients with ARVI, deterioration of IFN status up to suppression/depression of IFN system indicators in 1 patient with pneumonia (Covid-19), no dynamics in 5 patients with suppression of interferon status, complete normalisation of the response of the IFN system was noted only in 2 patients (13.3%).

4. CONCLUSION

The results of the conducted studies allow us to conclude that the inclusion of dietary supplements in the therapy of patients with mild and moderate forms of ARVI allows us to cope with the clinical symptoms of the disease in a shorter time and increase the effectiveness of the complex therapy, reducing the risk of complications and having a positive effect on the prognosis of the disease. The tolerability of the drug, according to the analysis of the patient questionnaire, was assessed as "very good", which confirms the high safety profile of the studied dietary supplement. The data obtained indicate a tendency towards normalization of the interferon status and the promising therapeutic potential of using the nutritional factor in the complex therapy of patients with ARVI, including COVID-19.

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