

*Originalni članci/  
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HERBAL MEDICINE IN ACUTE  
RESPIRATORY INFECTIONS  
BILJNI PROIZVODI U LEČENJU AKUTNIH  
RESPIRATORNIH INFEKCIJA

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*Key words*

mucus, cough, mucociliary clearance,  
secretolytic agents, pharmacological  
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*Ključne reči*

sekret, kašalj, mukocilijarni klirens,  
sekretolitik, farmakološki efekti.

*Abstract*

**Introduction and aim:** Herbal expectorants and secretolytic agents hold a sizeable share of the European market. Therefore it is essential to test their clinical effectiveness and safety. It has been known from centuries that herbal products have long been recognized to have an important role in natural defense of respiratory disease from various exogenous toxins.

In order to clarify the possible role of N-acetylcysteine (NAC) in the treatment of acute respiratory infections or exacerbations of chronic ones, we have carried out a study to assess the efficiency and safety of PropoMucil® in patients with various respiratory disease.

**Material and method:** The study was conducted from December 2016 to March 2017 in Belgrade, Serbia in five health care centers. The study included 904 patients suffered from various respiratory disease. All patients received natural products N-acetylcysteine combined with propolis to their additional therapy. We followed their symptoms on day 7th, 14th and after month ago.

**Results:** On the basis of the present assays, N-acetylcysteine combined with propolis (Propomucil®) have shown reduction of cough and mucus secretions in more than half patients on 7th day of usage of therapy. More than half patients (67,5%), on the 7th day check up had improvement in sputum production and its relieved. After a month of therapy with Propomucil®, only 7% have problems with persistent cough.

**Conclusion:** The study contributed to the evaluation of phytotherapy as a therapy of choice for relieve respiratory symptoms and its prevention. Results from our study have shown immense benefit (by reducing cough and dilution of sputum) of usage PropoMucil® in various respiratory disease.

*INTRODUCTION*

Acute respiratory tract infection (ARTI), which includes acute uncomplicated bronchitis, pharyngitis, rhinosinusitis, and the common cold, as well as worsening of symptoms of chronic disease such as asthma or chronic obstructive pulmonary disease is the most common reason for acute outpatient physician office visits <sup>(1)</sup>. Acute respiratory infection is a major cause of morbidity, hospitalization, and mortality with a worldwide disease burden estimated at 113 million disability-adjusted life years and 3.5 million deaths <sup>(2)</sup>. The diagnosis of acute respiratory infections is common and apparently easy to perform; however, the determination of the infection's causal agent is more complex, as current diagnostic tools are limited and rarely available in primary health care centers or even in hospitals in much of the world. Therefore, the infections are very frequently treated empirically and often successfully with antimicrobial therapy <sup>(2-3)</sup>.

The incidence of acute bronchitis in adults is high, between 30 and 50 per 1000 people per year. This means that in Europe, approximately 16 500 000 adult cases are seen each year in primary care. The clinical syndrome lasts approximately 2 weeks and has a clear impact on daily activities <sup>(3-4)</sup>. Proper and prompt management of respiratory infections is crucial.

Despite the fact that the majority of these infections being viral, a high percentage are treated with antibiotics <sup>(4)</sup>. A study from a large, outpatient ambulatory network of more than 52,000 cases of acute respiratory infections showed that antibiotics were prescribed in 65 percent of patients <sup>(5)</sup>. Overuse of antibiotics may lead to resistance, increased cost, and increased incidence of adverse effects, including anaphylaxis <sup>(4,5)</sup>. Bacterial superinfections of viral inflammations are rather frequent complications of viral respiratory tract inflammations, which only prolong the disease and

aggravate its course (6). Therefore, according to newest recommendations, the treatment of the acute respiratory infections should begin with relieving the symptoms involving antitussive medicines, decongestives, expectorants and antihistaminics.

Antibiotics are recommended only where there is scientific evidence that they are effective while the choice of therapy should be based on the culture and the sensitivity test results (targeted therapy) or on the known frequent pathogens present in such conditions or their current forms of resistance (empirical therapy). The antibiotic therapy is recommended by all means in cases of acute ear infections or mastoiditis. In case of exacerbations of chronic disease, antibiotics are second line of therapy (7).

In the light of new recommendations, herbal therapy found its place. N-acetylcysteine (NAC) is the acetylated variant of the amino acid L-cysteine and is widely used for various disease as supportive therapy. Some people use N-acetylcysteine for chronic bronchitis, chronic obstructive pulmonary disease (COPD), high fever, a lung condition called „fibrosing alveolitis”, head and neck cancer, and lung cancer (1,2,3). These clinical applications stem from its ability to support the body's antioxidant and nitric oxide systems during stress, infections, toxic assault, and inflammatory conditions. Supplementation with N-acetylcysteine has been shown to increase levels of glutathione, the body's major anti-oxidant (2). Glutathione is critically important for detoxifying an array of toxic substances, including xenobiotics (chemicals foreign to biologic systems), peroxide compounds, and other free radical-generating molecules. It thereby exerts a profound protective effect on cells (2,3). Of glutathione's three component amino acids (i.e., glutamate, glycine, and cysteine), cysteine has the lowest intracellular concentration. Because de novo synthesis is the primary mechanism by which glutathione is replenished, cysteine availability can limit the rate of glutathione synthesis during times of oxidative stress. Because the lungs are directly exposed to high levels of oxygen, there is no doubt that respiratory epithelium is a major target for oxidative injury that manifested in lung function changes including cough (4, 5).

By correcting or preventing glutathione depletion, N-acetylcysteine may ameliorate the inflammation that occurs in conditions such as various upper and lower respiratory disease and symptoms (asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, influenza, cough, acute bronchitis, pneumonia) and in addition to its antioxidant and expectorant actions, N-acetylcysteine acts as a vasodilator by facilitating the production and action of nitric oxide (6, 7).

Based on previous discussed products and the tendency to relieve symptoms in various disease, the aim of our study was to evaluate the efficacy and safety of combination N-acetylcysteine and propolis (PropoMucil®, combination of standardized propolis with 12% of polyphenol and N-acetylcystein; capsules or syrups, Abela Pharm, Belgrade, Serbia) in upper and lower respiratory infections.

#### METHOD AND PATIENTS:

The research was conducted as a prospective, clinical study in the period from Decemebtr 2016 to March 2017 by a phisicans of primary health centers from Belgrade (5 specialists in general medicine, 3 pulmonologists and 2 otorhinolaryngologists). A total of 904 patients participated in this study. The study included children older than 3 years and adults from 18 years old to more than 65ys old. Out of 904 patients, 453 were male and 442 female. All patients were asked about demographic characteristics (sex, age), smoking habit (current, former or nonsmokers at all) and their respiratory symptoms. A separate questionnaire for patients consist of questions about some characteristics of cough: whether the patient cough at first, when the cough is the most common and how often, do patients have problems with respiratory secretion during the day.

According to symptoms, they were treated by particular specialist. All participants have received PropoMucil® additionally to their main therapy. They used PropoMucil® capsules or syrups half hour before the breakfast. Control check- up was planned on 7<sup>th</sup> or 14 th day, or after a month and it was patients choice.

Separately, medical doctors were asked about their opinion of prescription dietetic supplement, why they prescribed if they do it, or no, and explanation for it.

The primary data obtained entered the SPSS 17.0 and were analyzed by descriptive statistical methods (mean, median, standard deviation and variation interval) and methods for testing data of clinical findings in two times (ANOVA).

#### RESULTS:

The study included 904 patients, equally divided in male and female (Figure 1). Most respondents were children under age of 5 years (291), then 6-18 ys (203) and older than 18ys (410) (Figure 2).

The patients had average  $1.29 \pm 0.55$  diagnosis (1 to 4 diagnosis), and most them had a diagnosis of upper respiratory tract infection (36.5%) and rhinitis / sinusitis (27.2%) (Table 1).

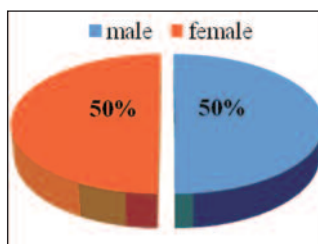


Figure 1. Distribution of patients by gender

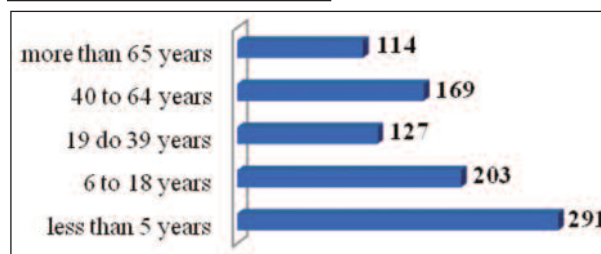


Figure 2. Distribution of patients by ages

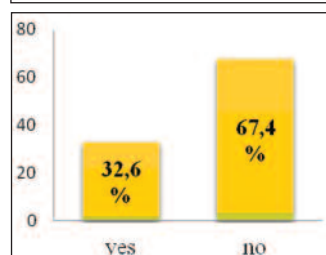


Figure 3. Distribution of smoking among patients

**Table 1.** Distribution of respiratory disease among patients

Diagnosis	n (%)
Upper respiratory tract infection	330 (36,5)
Lower respiratory tract infection	95 (10,5)
COPD	82 (9,1)
Bronhial asthma	124 (31,7)
Acute bronchitis	117 (12,9)
Otitis	114 (12,6)
Rhinitis/sinusitis	246 (27,2)

When it comes to the symptoms of the present disease, 795 subjects (87.9%) had a cough during the first visit. Most of the mentioned respondents (66.7%) suffered from multiple secretion during the course of the day, and the cough was most common in patients (44.4%) in the morning (Table 2). All respondents were on some type of medication therapy - 46.7% of them received antibiotic therapy, while the other 53.3% were on non-antibiotic therapy (Table 3). When it comes to antibiotic therapy, most respondents used penicillin antibiotics (37.9%), while in the case of non-antibiotic therapy, the use of nasal congestion (50.4%) was the most frequent (Table 3).

**Table 2.** Symptoms of main disease among patients

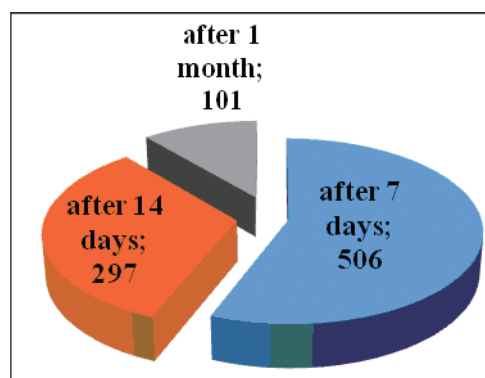
Symptomatology	n (%)
Whether the patient coughs?	
Yes	795 (87,9)
No	109 (12,1)
When is the cough most common?	
in the morning	353 (44,4)
in the evening	201 (25,3)
all the time	241 (30,3)
How often, during the day, patient is truggling with secretion?	
all the time	173 (21,8)
several times during the day	530 (66,7)
rarely	88 (11,1)
do not boder him	4 (0,4)

**Table 3.** Therapy of main disease

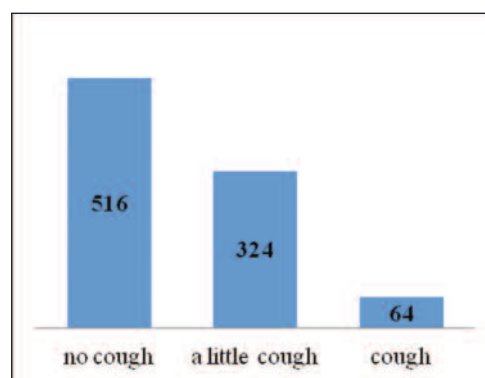
Therapy	n (%)
Antibiotic therapy	<b>422 (46,7)</b>
penicillins	160 (37,9)
cephalosporins	148 (35,1)
macrolides	62 (14,7)
another group of antibiotics	52 (12,3)
Non-antibiotic therapy	<b>482 (53,3)</b>
nasal congestives	243 (50,4)
antihistaminics	89 (18,5)
bronchodilators	105 (21,8)
corticosteroids	45 (9,3)

To all patients were given PropoMucil®, with regular antibiotic or non-antibiotic therapy up to control. The control examination was performed after 7 days to a month, from the first visit to the doctor (Figure 4). However, the highest number of patients (55.9%) came to the checkup

after 7 days of their first visit to the doctor (Figure 4). Even 57.1% of the them did not complain about coughing (Figure 5).



**Figure 4.** Distribution of patients in terms



**Figure 5.** Distribution of patients in terms of control examination of cough on control examination

At the first and the control, the quality of the secretion was registered, with a statistically significant difference (Table 5). Almost half of the patients (46.6%) had a viscous, i.e. thick secretion at the first examination, while 67.5% of the subjects did not have secretion (Table 5).

**Table 5.** The quality of the secretion on the first and control examination of patients

Quality of secretion	First examination n (%)	Control examination n (%)	Significance (p)*
no secret	15 (1,7)	610 (67,5)	
Fluent	253 (27,9)	206 (22,8)	0,000
viscouse, thick	421 (46,6)	84 (9,3)	
thick, sticky	215 (23,8)	4 (0,4)	

p- statistical significant; \*ANOVA

Asked by doctors why they decide to prescribe dietetic supplement PropoMucil®, in 60% of them replied that it was effective in reducing the secretion (sputum), while on the question of which is the biggest obstacle for patients to significantly increase the use of supplements 80% of them claimed the current product price (Figure 6 and 7).

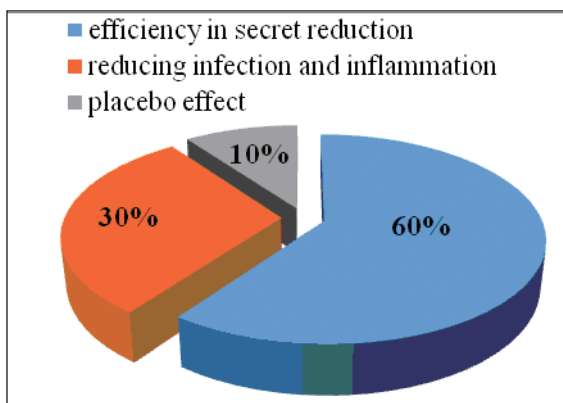


Figure 6. The reasons for prescribing the

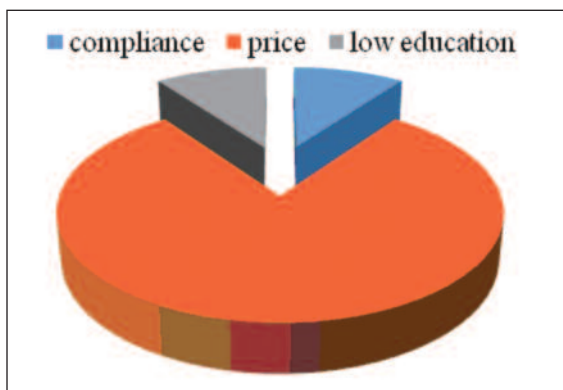


Figure 7. The reasons for obstacle for dietary supplement to patients more significant use of dietary supplement

## DISCUSSION

Our study included overall 904 (equally divided by sex distribution) participants who used PropoMucil® as an additional therapy. Among them, 32,6 participants consumed nikotine, while 67,4 were non smokers. Most patients had upper respiratory infection (49,4%), bronchial asthma (31,9%), rhinitis/sinusitis (27,2%), ear inflammation (12,6%), lower respiratory infection (10,5%), chronic obstructive pulmonary disease (COPD) (9,1%), respectively. Leading symptom which brought them to doctor was cough in 87,9% participants, mostly in the early morning hours. Apart cough, 66,7% patients complained for mucus secretion for whom they could not breathe. Recent clinical and experimental studies have emphasized the upregulation (sensitization) of cough in pathological conditions of airways. The peripheral mechanisms of increased cough sensitivity during airway diseases include the potential role of inflammatory mediators, neutrophils, and changes in airway mucosal structure (7, 8). In that cases, the role of mucolytic drugs is immense, apart from other benefits. Patients felt more relieved when using mucolytic agents which help them breathe. Our research is in accordance to previous studies which emphasize the role of N-acetylcysteine in chronic conditions. The strong signal comes from various meta-analysis that if a patient suffering from chronic bronchitis presents a documented airway obstruction, NAC should be administered at a dose of  $\geq 1200$  mg per day to prevent exacerbations, while if a patient suffers from chronic bronchitis, but is without airway obstruction, a regular treatment of 600 mg per day seems to be sufficient (9).

Also, previous results have reported that 100% oxygen plays a key role in the development of airway and lung damage, which brings about a down-regulation of cough reflex. Cough is normal, defending act of an organism and it is desirable to cough because the recovery time is faster (8, 9). Because oxidative stress is involved in the pathophysiology of inflammatory airways diseases, we can surmise that supplemented antioxidants could mitigate the oxidant status, inflammatory cytokines or gene expression, and thus could be of clinical benefits (10, 11).

More recently, animal and human studies on N-acetylcysteine have shown it to be a powerful antioxidant and a potential therapeutic agent in the treatment of upper and lower respiratory diseases, cancer, heart disease, heavy metal toxicity, and other diseases characterized by oxidant-antioxidant imbalance (11, 12). Historically, NAC has been used as a mucolytic and expectorant agent in chronic respiratory illnesses (10). All patients used some medication for their primary disease. Antibiotics were received 46,7% patients, while 53,5% used some kind of other therapy, mostly intranasal corticosteroids (50,4%). Among used antibiotics, penicillin was the most prescribed drug.

All participants have received PropoMucil® additionally to their main therapy. They used PropoMucil® capsules or syrup half hour before the breakfast. Control check-up was planned from 7th day of therapy up to one month, depending on patients choice. Still, the most patients came on 7th day after therapy (55, 9%). Among them, 57,1% patients had not complaint for cough, nor is the same register on the spot. Statistical significance was remarked between first and control check-up ( $p < 0.01$ ). Namely, almost half of patients (46,6%) had viscous thick secretion on first visit, while it was not present on check-up examination after 7, 14 and one month in 67,5% patients. Here, we could register a beneficial role of using mucolytic drugs. More than half investigated patients felt better after 7 days of therapy with PropoMucil® when they decided to check up for their symptoms. On control examination, whether it was on 7th, 14 days or after a month ago, cough was not present in 516 patients, 324 patients reported a little late, while 64 patients cough persistently (7%). We should bear in mind that patients used a standard dose of PropoMucil®, and we reached positive effects in 75,93% patients during only 7 days of usage. This founding arise a new questions about a doses and duration of recommended N-acetylcysteine in rest of 24% patients.

Also, our research included the survey about doctors opinion on effects of PropoMucil® in every day work. They claimed that their experience with PropoMucil® is very well and it had been proven as a good secretolytic agent, but compliance between doctor and patient was very poor, due to price of product (just 10% of patients had good compliance).

Results of our study had shown that PropoMucil® has good clinical efficacy in reduction of patients symptoms, predominantly cough and production of sputum. These findings may probably be due to the pH of the medium which permitted different redox potential of the propolis antioxidant compounds, and also due to the different kind of radicals formed, allowing mucolytic effect (13, 14, 15). Previous

studies has been postulated that antioxidants may influence the expression of hyperoxia-induced lung injury. Many recent studies demonstrate that antioxidants, by virtue of anti-inflammatory effects protect the respiratory system in a model of oxidative lung injury (16, 17, 18). The relationship between airway oxidative damage and supplementation of antioxidant substances is still unclear and many findings are controversial (19, 20, 21).

#### CONCLUSION:

We found that PropoMucil® has the strong mucolytic effect which was demonstrated in reduction of cough and sputum production at a very 7th day of its usage. Results from our study have shown immense benefit (by reducing cough and dilution of sputum) of usage PropoMucil® in acute as well as exacerbation of chronic respiratory diseases. Furthermore, since propolis and its constituents were widely effective as an antioxidant, it may be expected that PropoMucil® have beneficial effects against at least some oxidative stress-related diseases.

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### Sažetak

**Uvod:** Biljni ekspektoransi i sekretolitički agensi imaju značajan udeo u evropskom tržištu. Zbog toga je neophodno testirati njihovu kliničku efikasnost i sigurnost. Od davnina je poznato da biljni proizvodi imaju protektivnu ulogu u respiratornom sistemu. Da bi se razjasnila moguća uloga N-acetilcisteina u lečenju akutnih respiratornih infekcija ili pogoršanja postojećih hroničnih, ovom studijom testirali smo efikasnost i sigurnost preparata Propomucil® u gore navedenim oboljenjima.

**Materijal i metode:** Studijom je obuhvaćeno ukupno 904 pacijenta koji su lečeni od različitih respiratornih oboljenja u 5 zdravstvenih centara u periodu od decembra 2016. godine do marta 2017. godine. Svaki pacijent je pored osnovne terapije dobio i dodatnu u vidu Propomucil®-a. Simptomi bolesti su praćeni nakon 7, 14 ili mesec dana terapije.

**Rezultati:** Smanjenje kašlja i mukozne sekrecije registrovano je već 7 dana od početka terapije kod više od pola ispitivanih pacijenata. Takođe, kod više od pola ispitivanih pacijenata (67,5%) pokazalo se poboljšanje u produkciji sputuma i njegovoj eliminaciji, pri čemu su se pacijenti značajno bolje osećali. Kod samo 7% pacijenata, nakon primenjene terapije, zadržao se kašalj.

**Zaključak:** Sprovedena studija doprinela je oceni fitoterapije kao terapije izbora za ublažavanje respiratornih simptoma. Rezultati naše studije pokazali su dobit (smanjenje kašlja i viskoznosti sputuma) upotrebom Propomucil®-a već 7.-og dana terapije kod obolelih od akutnih ili pogoršanja hroničnih respiratornih oboljenja.

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