



Treatment of Respiratory Tract Infections with a Pelargonium sidoides Extract (EPs[®] 7630)

- Literature study

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Abstract

Introduction: Respiratory tract infections refer to a range of frequent diseases of the upper respiratory tract and lower respiratory tract. It is one of the most common health complaints for which people seek primary care. Respiratory tract infections can be caused by viruses or bacteria [1]. Common cold is the most common reason to seek out natural remedies in Sweden. Sales of natural remedies in 2003 amounted to about SEK 900 million in consumer price [2]. Annual revenues for traditional medicinal products in Western Europe reached US\$ 5 billion in 2003-2004[3]. Since indications for traditional herbal medicinal products are based mainly on the experience of longstanding use and there are no requirements for clinical studies prior to the registration of traditional herbal medicinal products, therefore this is an interesting topic to study.

Objective: The aim of this degree project is to carry out a literature study in order to answer the following questions: Is Pelargonium sidoides extract (EPs[®] 7630) effective against viruses or bacteria that cause respiratory tract infection? Are there clinical significant effects of extract (EPs[®] 7630)? Are there interactions associated with extract (EPs[®] 7630)? Are there adverse events associated with extract (EPs[®] 7630)?

Methods: The search for material was conducted in the database MEDLINE via PubMed. Search on the Internet was also performed by using the search engine Google.

Results: All the six studies utilized in the clinical evidence section of this literature study were multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial. The studies were conducted in Russia and Ukraine. The eligible participants in each study group were between 103 and 406 (male and female patients) which received randomized treatment for a period of 7 or 10 days. The results of the studies confirmed that EPs[®]7630 was superior in efficacy compared to placebo. Extract EPs[®]7630 considerably reduced the severity of individual symptoms and shortens the duration of the sicknesses (common cold and acute bronchitis). Furthermore, the two in vitro studies used in this literature study showed that extract EPs[®] 7630 was effective against viruses or bacteria that cause respiratory tract infection.

Conclusion: Pelargonium sidoides extract EPs[®] 7630 appears to be an effective treatment for respiratory tract infection based on the findings in this literature study.

Keywords: Respiratory tract infection, pelargonium sidoides, EPs[®] 7630, placebo, common cold, acute bronchitis.

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1. Introduction

In Sweden, respiratory tract infection (RTI) is one of the most common health complaints for which people seek primary care. Respiratory tract infections refer to a range of frequent diseases of the upper respiratory tract or lower respiratory tract. It can be caused by viruses or bacteria [1].

Upper respiratory tract infection (URI) is a collective name for the most frequent diseases of the respiratory system such as common cold, laryngitis, pharyngitis, rhinitis, sinusitis and tonsillitis. Upper respiratory tract infection is usually caused by rhinovirus, but there are also other viruses which cause upper respiratory tract infection, including coronavirus, human parainfluenza viruses, human respiratory syncytial virus, adenovirus and enterovirus [1].

Common cold is the most common reason to seek out natural remedies in Sweden. Sales of natural remedies in 2003 amounted to about SEK 900 million in consumer price [2]. Annual revenues for traditional medicinal products in Western Europe reached US\$ 5 billion in 2003-2004[3].

The two most frequent lower respiratory infections (LRIs) are bronchitis and pneumonia. Bronchitis is a common disease that is usually caused by viral infections. This leads to the mucous membranes of the bronchial tubes swell and produce more mucus than usual [4]. Bronchitis can be divided into two categories such as acute and chronic bronchitis. Pneumonia means that the small air-filled bladders in the interior of the lungs become inflamed. This inflammation of the lung is often caused by bacteria or viruses [5].

Since indications for traditional herbal medicinal products are based mainly on the experience of longstanding use and there are no requirements for clinical studies prior to the registration of traditional herbal medicinal products, therefore this is an interesting topic to study.

1.1 Presentation of Pelargonium sidoides

Pelargonium reniforme and Pelargonium sidoides belong to the same genus pelargonium which includes other species of the Geraniaceae family. The two species are closely related and can be distinguished from each other by the shape and colour of the petal [6].

Pelargonium sidoides is an indigenous medicinal plant of South Africa. The extract from the roots of Pelargonium sidoides has been used traditionally for the treatment of various symptoms of respiratory tract infections.

Kaloba® (film-coated tablet) is a registered trademark by Dr. Willmar Schwabe GmbH & Co KG, Karlsruhe, Germany containing the extract (EPs[®] 7630) from the roots of Pelargonium sidoides. It was registered in Sweden, May 2009 by the Swedish Medical Products Agency as a traditional herbal medicinal for the relief of the symptoms of common cold, such as sore throat, cough and runny nose [7].

Trecura oral drop (trademark by Cederroth AB) is another traditional herbal medicinal with active substance of *Pelargonium sidoides* that was registered in Sweden, July 2011 by the Swedish Medical Products Agency. Trecura was registered with approved indication for the relief of the symptoms of common cold, such as sore throat, cough and runny nose [8]. Presently, Trecura is not available in Sweden.

1.2 Botany

Pelargonium sidoides forms a rosette-like plant with thickened underground roots and sparsely branched stems from the base. At flowering, the velvety stem is about 20-50 cm high carrying the heart-shaped leaves tangentially to its length [9]. It is commonly found throughout the Eastern Cape, Lesotho, Free State and Southern and South-Western Gauteng in South Africa.



Figure1 [10]

1.3 Traditional use

Pelargonium sidoides has been traditionally used for hundreds of years by the Zulu, Basuto, Xhosa and Mfenfi people in South Africa as a healing for coughs, upper respiratory tract irritations, tuberculosis and gastrointestinal concerns. Its common names include Umckaloabo and South African Geranium. The name Umckaloabo is derived from two Zulu words: umkhuhlane (fever and cough-related diseases) and uhlabo (pleurisy-related chest pain), representing the indication for use [6].

1.4 Historical and Modern uses

Charles Stevens (an Englishman born in 1880) at age 17 consulted his doctor with chest symptoms. His doctor advised him to visit South Africa to find a cure [11]. In 1897, Charles Stevens travelled to South Africa with the hope to find a cure for his respiratory illness. In

South Africa, he was treated by a traditional healer. Stevens believed that he recovered from tuberculosis by the administration of a decoction of umckaloabo prepared by a traditional healer [11, 12].

Pelargonium sidoides became famous in 1930 with the publication of ‘The treatment of tuberculosis with umckaloabo (Stevens’ Cure)’ by Adrien Secheyay from Geneva. Altogether over the next nine years he treated more than 800 patients in Switzerland with a homeopathic preparation of Pelargonium sidoides roots. He concluded that, while not infallible, the cure was a definite advance in treatment of tuberculosis [11]. Pelargonium sidoides remains a popular herbal remedy in parts of Europe. But with the advent of synthetic drugs, the remedy was forgotten by Western medicine until its recent rediscovery by European researchers [13].

In Germany, a standardized extract of Pelargonium sidoides (EPs[®] 7630) was registered in 2005 by the Federal Institute for Drugs and Medical Devices (BfArM) for the indication “acute bronchitis” [14].

1.5 The main active constituents

“A Detailed View on the Constituents of EPs[®] 7630” [15]

EPs7630 is an extract of Pelargonium sidoides. The extract (EPs[®] 7630) is produced by extraction of grinded dried roots of Pelargonium sidoides, extraction solvent: ethanol 11% (w/w). This solvent leads to a spectrum of constituents which differs significantly from extracts obtained by extraction with non-polar solvents [15].

Extract (EPs[®] 7630) of Pelargonium sidoides comprises of six major groups of components such as substituted benzopyranones, purine derivatives, peptides, minerals, unsubstituted and substituted oligomeric prodelphinidins, monomeric and oligomeric carbohydrates.

Pharmacologically active substances of EPs[®] 7630 are amongst other oxygenated coumarins (e.g. umckalin) and polyphenolic compounds [16].

In addition, the compositional profile of extract (EPs[®] 7630) consists of: around 40% of oligomers of the proanthocyanidin family (based on gallicocatechin and epigallocatechin entities), 12% minerals, 12% carbohydrates, 2% benzopyranones (e.g. umckalin, 5, 6-dimethoxy-7, 8-dihydroxycoumarin and 6, 7, 8-trihydroxycoumarin), 2% purins, 22% unknowns, 10% amino acids and peptides [15].

1.6 Mechanism of Action

The mechanism of action of Pelargonium sidoides extract EPs[®] 7630 is not fully known. The following are some of its pharmacological activities; inhibition of the interaction between group A-streptococci and host epithelia and interference with replication of different respiratory viruses (see 3.1.1 and 3.1.2 for more detail of the two mentioned pharmacological

activities). Moreover, Pelargonium sidoides extract EPs[®] 7630 also improves phagocytosis, oxidative burst and intracellular killing of human peripheral blood phagocytes [16].

1.7 Objective

The purpose of this degree project is to carry out a literature study in order to answer these following questions:

- Is Pelargonium sidoides extract (EPs[®] 7630) effective against viruses or bacteria that cause respiratory tract infection?
- Are there clinical significant effects of Pelargonium sidoides extract (EPs[®] 7630)?
- Are there interactions associated with Pelargonium sidoides extract (EPs[®] 7630)?
- Are there adverse events associated with Pelargonium sidoides extract (EPs[®] 7630)?

2. Material and Methods

The search for material was carried out in the database MEDLINE via PubMed between 19 January and 28 February 2013. Details of the search information are presented in (Table 1). The search for information on the Internet was also conducted by using the search engine Google. Keywords used were as follows:

- pelargonium sidoides
- pelargonium sidoides AND respiratory tract infections
- pelargonium sidoides AND constituents
- pelargonium sidoides AND interactions
- pelargonium sidoides AND allergic

The criteria for the selection of articles were as follows: original article, numbers of participants, randomized, double-blind and placebo-controlled clinical trial. In this literature study, ten original articles have been used in the result section and also as basis in the discussion section. Information retrieved from the Internet and course books were only utilized in the introduction section.

Table 1 *Details of the search information.*

Date	Keywords	Results	Chosen article	Original article	Review article	Article Number
22/01/2013	pelargonium sidoides	65	4	4		23, 16, 18 and 19
28/01/2013	pelargonium sidoides AND respiratory tract infections	40	4	4		17, 20, 21 and 22
30/01/2013	pelargonium sidoides AND constituents	11	1	1		15
4/02/2013	Pelargonium sidoides AND interactions	10	2	2		14, and 24
25/02/2013	Pelargonium sidoides AND allergic	1	1	1		6

3. Results

3.1 In vitro studies

3.1.1 Conrad et al [17]:

The primary aim of this in vitro study was to investigate the impact of Pelargonium sidoides extract EPs[®] 7630 on group A-streptococci (GAS) adhering to and invading host epithelial cells [17]. The study was carried out by Conrad et al. Streptococcus pyogenes was test organism in this study. EPs[®] 7630 (doses between 0 and 30 microgram/ml) was applied to the both test systems.

Furthermore, the flow cytometric assay was used to examine adhesion of A-streptococci (GAS) on Human epidermoid cancer cells (Hep-2) and blood endothelial cell (BEC). From the flow cytometric investigations of A-streptococci (GAS) adherence to Hep-2, it was revealed that after 120 min of co-incubation, EPs[®] 7630 concentration dependently reduced bacterial attachment. In control samples without EPs[®] 7630, test organisms attachment occurred to over 80% of Hep-2, whereas adhesion was reduced on average by over 46% when 30 microgram/ml EPs[®] 7630 was added [17].

Moreover, in the kinetic experiments that was conducted regarding impact of EPs[®] 7630 on GAS adhesion kinetic, the kinetic curves deceased very quickly in the presence of EPs[®] 7630 compared with the controls in the further course of the experiment. The reduction in bacterial adhesion was more obvious when 30 microgram/ml EPs[®] 7630 was added and during co-incubation period of 180 min. EPs[®] 7630 considerably reduces GAS attachment to epithelial cell according to this experiment.

In addition, it was observed that 30 microgram/ml EPs[®] 7630 reduced streptococcal invasion of epithelia, in experiments based on the penicillin-/gentamicin-protection assay in order to assess intracellular bacteria.

3.1.2 Michaelis et al [14]:

This in vitro study was performed by Michaelis et al. The purpose of the study was to investigate the influence of Pelargonium sidoides extract EPs[®] 7630 on replication of a panel of respiratory viruses [14].

EPs[®] 7630 was tested on these following viruses: adenovirus 3, adenovirus 7, respiratory syncytial virus (RSV), parainfluenza virus 3, human rhinovirus 16, H1N1 influenza, H3N2 influenza, H5N1 influenza, coronavirus (HCo-229E) and Coxsackie virus A9.

Additionally, it was observed that EPs[®] 7630 interfered with virus-induced cytopathogenic effect (CPE) caused by respiratory syncytial virus (RSV), coronavirus (HCo-229E), H1N1 influenza, H3N2 influenza, parainfluenza virus3, or coxsackie virus A9. However, 100 microgram/ml EPs[®] 7630 showed non-significant advantage (decrease was not noticed) in viability of all examined cell types. Besides, EPs[®] 7630 failed to affect virus-induced cytopathogenic effect (CPE) induced by adenovirus 3, adenovirus 7, H5N1 influenza, or human rhinovirus 16 in the investigated concentrations (up to 100 microgram /ml).

Moreover, the influence of EPs[®] 7630 was examined on H1N1 influenza, H3N2 influenza, respiratory syncytial virus (RSV), coronavirus (HCo-229E), parainfluenza virus 3, or coxsackie virus A9 virus titres. From the investigation, EPs[®] 7630 reduced titres of all susceptible viruses in a dose-dependent manner [14].

3.2 Clinical evidence

3.2.1 Study 1

“Efficacy of a *Pelargonium sidoides* preparation in patients with the common cold: a randomized, double blind, placebo-controlled clinical trial” [18]:

From December 2003 to May 2004, Lizogub et al. performed this randomized, double blind, placebo-controlled clinical trial in eight outpatient departments in the Ukraine. The aim of the study was to evaluate the efficacy of a liquid herbal drug preparation from the roots of *Pelargonium sidoides* in patients with the common cold [18].

The inclusion criteria used in the clinical trial were as follows; age between 18 and 55 years, written agreement, participant must have at least two main cold symptoms (sore throat, nasal discharge) and one minor cold symptom (hoarseness, scratchy throat, cough, nasal congestion, headache, sneezing, muscle aches, and fever) or indication of one main and at least three minor cold symptoms, with cold symptoms lasting 24 to 48 hours. The participants (103 male and female patients) who met the inclusion criteria were involved in the clinical trial;

Furthermore, the following are some of the exclusion criteria applied in the trial; indication of any other acute throat, nose, ear and respiratory tract disease than the common cold, for example, bronchitis sinusitis, tonsillitis, allergic rhinitis, otitis, et cetera.

After randomization, the eligible male and female patients were recommended to use EPs[®] 7630 at 30 drops (1.5mL) three times daily, 30 minutes before or after a meal for period of 10

days, or a matched placebo for the same period. Patients were also allowed to take 500 mg paracetamol if fever equal to or over 39 degrees Celsius occurs during the trail.

The primary assessment criterion for outcomes was based on the sum of symptom intensity differences (SSID) of the cold intensity score (CIS) beginning at day one, continuing to day five. The cold symptoms used for the cold intensity score (CIS) comprised of hoarseness, cough, sore throat, scratchy throat, nasal drainage, nasal congestion, sneezing, headache, muscle aches, and fever. At day one, a small difference in total cold intensity score (CIS) was observed in both treatment groups (EPs[®] 7630 group with 17.8±4.0 compared to 16.9±3.4 in placebo group). At day five, mean total cold intensity score (CIS) declined by 10.4 ±3.0 points in the EPs[®] 7630 compared to a decline of 5.6±4.3 points in the placebo group.

In addition, significant improvement in mean sum of symptom intensity differences (SSID) was noticeable at day five. The EPs[®] 7630 group improved by 14.6 ± 5.3 points compared to 7.6 ±7.5 points in placebo group.

The secondary measurement criteria for efficacy comprise of these following aspects: different response criteria in accordance with the total cold intensity score (CIS), alteration of individual symptoms, work capacity, treatment outcome and health-related quality of life. From day one to day ten, mean diminished were observed in both main and minor individual symptoms of cold intensity score (CIS). Besides, mean declined was obviously higher in the EPs[®] 7630 group than in the placebo group. In the EPs[®] 7630 group the rates of responders were higher than in the placebo group. Also, rates of patients with clinical cure were higher in the EPs[®] 7630 group (78.8%) than in the placebo (31.4%).

From day one to day five, the rates of remission and improvement in further cold-relevant symptoms were significantly higher in the EPs[®] 7630 group compared to placebo group (Table 2).

Table 2 Rates of remission and improvement in the EPs[®] 7630 compared to placebo group (data collected from [18]).

Symptoms	EPs [®] 7630 percentage of patients	Placebo percentage of patients
Limb pain	95.5%	73.8%
Weakness all over	78.9%	35.3%
Exhaustion	84.6%	43.1%
Fatigue	89.4%	60.5%

Moreover, in the EPs[®] 7630 group, the mean duration of incapability to work was significant lower compared to placebo group (6.9 ± 1.8 days versus 8.2 ± 2.1 days). According to integrative medicine outcomes scale (IMOS), complete recovery or major improvement at day five were higher in the EPs[®] 7630 group (33 of 52 patients 63.4%) compared to placebo group (2 of 51 patients 3.9%). The outcome for general well-being from day one to day five was obviously higher in the EPs[®] 7630 group (94.2%) compared to placebo group (68.6%). In the EPs[®] 7630 group, 86.5% of patients reported that they were very satisfied or satisfied with treatment compared with 41.2% of patients in the placebo group.

3.2.2 Study 2

“Treatment of acute bronchitis in adults with a Pelargonium sidoides Preparation (EPs[®] 7630): a randomized, double-blind, placebo-controlled trial” [19]:

Chuchalin et al. conducted this multicenter, prospective, randomized, double-blind, placebo-controlled trial from April 2000 to March 2001 at six urban primary care outpatient clinics in Russia. The purpose of the study was to evaluate the efficacy and safety of preparation from the roots of Pelargonium sidoides (EPs[®] 7630) compared with placebo in patients with acute bronchitis [19].

The 124 male and female patients who fulfilled the inclusion criteria were accepted in the trial. Inclusion criteria for the study were as follows: patients with acute bronchitis with a Bronchitis Severity Score (BSS) ≥ 5 points, symptoms beginning ≤ 48 hours and age ≥ 18 years.

Besides, some of the exclusion criteria were as follows: evidence for antibiotic treatment or treatment with antibiotics during the past 4 weeks before the starting of the trial, tendency to bleed; severe heart, renal, or liver diseases; immunosuppression, et cetera. After scrutiny, qualified patients were randomly assigned to receive either 30 drops (1.5mL) of EPs[®] 7630 or placebo 3 times per day, 30 minutes before or after meals was recommended for 7 consecutive days.

The primary measurement criterion for evaluating the efficacy of EPs[®] 7630 compared with placebo was the alteration in bronchitis severity score (BSS) total score at day 7 of treatment. Bronchitis severity score (BSS) total score comprised of the five most important attributes connected with acute bronchitis such as sputum, rales/rhonchi, chest pain during coughing, cough and dyspnea. In addition, bronchitis severity scores (BSS) for both treatment groups were very much alike at day one (baseline). At day seven, bronchitis severity score (BSS) diminished by 7.2 ± 3.1 points in the EPs[®] 7630 compared to a decrease of 4.9 ± 2.7 points in the placebo group.

The secondary assessment criteria for efficacy were based on these following conditions: bronchitis severity score (BSS) < 5 points at day seven of treatment, decline of bronchitis severity score (BSS) \geq 5 points between day one and day seven, patients treatment outcome, onset of treatment effect and health-related quality of life. In the EPs[®] 7630 group, bronchitis severity score (BSS) < 5 points noticed in 61 of 64 patients (95.3%) compared to 35 of 60 patients (58.3%) in the placebo group.

At day seven, diminished in BSS of at least 5 points was noticed in both treatment groups, 58 of 64 patients (90.6%) in EPs[®] 7630 group and 31 of 60 patients (51.7%) in placebo group. Rapid recovery in 58 of 64 patients (90.6%) in the EPs[®] 7630 group was pronounced compared to 25 of 60 patients (41.7%) in the placebo group. Regarding the five individual symptoms, the rates of recovery for symptoms rales/rhonchi, chest pain during coughing and dyspnea were above 90%. The rate of recovery in cough was very slow in both treatment groups, 20 of 64 patients (31.3%) in the EPs[®] 7630 group compared to 3 of 60 patients (5.0%) in the placebo group.

Additionally, in the further clinical symptoms at day 7, EPs[®] 7630 exhibited the highest recovery rates in all five supplementary symptoms (**Table 3**).

Table 3 Recovery rates in the EPs[®]7630 group compared to placebo group in further clinical symptoms at day seven (data collected from [19]).

Symptoms	EPs [®] 7630 percentage of patients	Placebo percentage of patients
Fever	93.2%	82.9%
Pain in the limbs	92.9%	76.9%
Headache	86.7%	77.8%
Fatigue/exhaustion	84.1%	66.1%
Hoarseness	77.6%	38.5%

Moreover, at day seven, the outcome for better quality of life after treatment was obviously higher in the EPs[®] 7630 group (61.9%) compared to placebo group (41.4%). In the EPs[®] 7630 group, 32.8% of patients regained a lot of energy at day 7 compared to (25.4%) of patients in placebo group. More patients in the EPs[®] 7630 group (51 of 64 patients (79.7%)) reported that they were satisfied with the treatment compared to (26 of 60 patients (43.3%)) in the placebo group.

3.2.3 Study 3

“Efficacy and tolerability of EPs[®] 7630 in patients (aged 6–18 years old) with acute bronchitis” [20]:

Between February and May 2006, this randomized, double-blind, placebo-controlled clinical dose-finding study was carried out at 16 centres in Ukraine by Kamin et al [20]. The primary objective of the study was to demonstrate the efficacy and to evaluate the safety and tolerability of three doses of EPs[®] 7630 in acute bronchitis [20].

The following inclusion criteria were utilized in this study: patients with acute bronchitis with bronchitis specific symptoms (BSS) ≥ 5 points, symptoms beginning ≤ 48 hours and age between 6 and 18 years. The participants (total of 400 male and female) patients between 6 and 18 years who met the inclusion criteria were included in the trial.

In addition, the following are some of the exclusion criteria applied in this study: indication for antibiotic treatment, bronchodilators or glucocorticoids during the past four weeks before the starting of the trial, tendency to bleed; severe heart, renal, or liver diseases; immunosuppression, et cetera. After randomization, the suitable patients were instructed to take 30 mg EPs[®] 7630, 60 mg EPs[®] 7630 or 90 mg EPs[®] 7630, 30 minutes before or after a meal continuously for 7 days, or a matched placebo for 7 consecutive days.

The primary evaluation criterion for assessing the efficacy of EPs[®] 7630 compared with placebo was alteration in bronchitis specific symptoms (BSS) total score at day 7 of treatment. Bronchitis specific symptoms (BSS) total score comprised of the five most important features connected with acute bronchitis such as chest pain during coughing, cough, sputum, pulmonary rales at auscultation, and dyspnea. Scale of bronchitis specific symptoms (BSS) total score was rated from 0 (not present) to 4 (very severe) and maximum point was 20 (4*5 features).

Furthermore, at day 7, decline in BSS was observed in both treatment groups (**Table 4**). Additionally, significant difference in the BSS total score for the 60 mg EPs[®] 7630 and 90 mg EPs[®] 7630 was noticed from day 3 to day 7.

Table 4 *Decrease in the bronchitis specific symptoms (BSS) total score from day 0 to day 7 (data collected from [20]).*

30 mg EPs [®] 7630	60 mg EPs [®] 7630	90 mg EPs [®] 7630	Placebo
3.6 ± 2.4	4.4 ± 2.4	5.0 ± 1.9	3.3 ± 2.6

In addition, some of the secondary measurement criteria for evaluating the efficacy of EPs[®] 7630 were as follows: bronchitis specific symptoms (BSS) total score < 3 points at day seven of treatment, decline in bronchitis specific symptoms (BSS) total score at least 7 points between day 0 and day 7, treatment outcome and onset of treatment effect. The EPs[®] 7630 group was higher in the treatment response calculated on the basis of the bronchitis specific symptoms (BSS) total score compared to placebo group.

Remarkable difference was observed in the 60 mg EPs[®] 7630 and 90 mg EPs[®] 7630 compared to placebo group. Also, a significant difference was noticed in the rate of responders in the EPs[®] 7630 groups compared to placebo group (**Table 5**).

Table 5 Rate of responders at day 7 according to all three response criteria (data collected from [20]).

Criterion	30 mg EPs [®] 7630 Percentage of patients	60 mg EPs [®] 7630 Percentage of patients	90 mg EPs [®] 7630 Percentage of patients	Placebo Percentage of patients
Criterion 1 BSS total < 3 points at day 7	36%	57%	73%	42%
Criterion 2 Decrease in BSS total score of at 7 points from day 0 to day 7	11%	17%	22%	10%
Criterion 3 Combination of criteria 1 and 2	9%	17%	22%	9%

Besides, the onset effect was higher in the EPs[®] 7630 group and patients in the EPs[®] 7630 groups were satisfied or very satisfied with the treatment in accordance with integrative medicine patient satisfaction scale (IMPSS). Percentages of patients that regained energy and returned to school or work were higher in the EPs[®] 7630 group compared to placebo group (**Table 6**).

Table 6 Percentage of patients able to attend kindergarten, school or work at day 7 (data collected from [20]).

30 mg EPs[®] 7630 Percentage of patients	60 mg EPs[®] 7630 Percentage of patients	90 mg EPs[®] 7630 Percentage of patients	Placebo Percentage of patients
35.0%	44.4%	53.5%	33.7%

3.2.4 Study 4

“Treatment of acute bronchitis with a liquid herbal drug preparation from *Pelargonium sidoides* (EPs[®] 7630): a randomized, double-blind, placebo-controlled, multicenter study” [21]:

This multicenter, prospective, randomized, double-blind, placebo-controlled study was conducted in Russia from 2 October 2000 to 19 March 2002 by Matthys et al. The objective of this study was to examine the efficacy and safety of EPs[®] 7630 in the treatment of acute bronchitis in adults [21].

The 217 male and female patients aged 18 – 66 years who fulfilled the inclusion criteria were involved in the clinical trial. Inclusion criteria for the study were as follows: concession, aged 18 – 66 patients suffering from acute bronchitis with a Bronchitis Symptom Score (BSS) >5 points and duration of complaints <48 hours.

Additionally, some of the exclusion criteria were as follows: evidence for antibiotic treatment or treatment with antibiotics during the past four weeks before the starting of the trial; allergic bronchial asthma; tendency to bleed; severe heart, renal, or liver diseases; immunosuppression, et cetera. After scrutiny, acceptable patients were randomly assigned to receive either 30 drops EPs[®] 7630 or a placebo 3 times per day at least 30 minutes before or after meals for a period of 7 days. Patients were also allowed to take 500 mg paracetamol if fever equal to or over 39 degrees Celsius occurs during the trial.

The primary measurement criterion for assessing the efficacy of EPs[®] 7630 -solution compared to placebo was the alteration in bronchitis symptom score (BSS) between day 0 and day 7 of treatment. Bronchitis symptom score (BSS) was established on five rating: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) for the five most essential characteristics connected with acute bronchitis such as cough, rales/rhonchi, chest pain during coughing sputum, and dyspnea. Between day 0 to day 7, declined in bronchitis symptom score was observed in both treatment groups, the decrease was more notable in the EPs[®] 7630 group (7.6 ± 2.2 (8.0) points) compared to placebo group (5.3 ± 3.2 (6.0) points).

The rate of complete recovery was higher in the EPs[®] 7630 group (89.8%) compared to placebo group (65.1%). Furthermore, for each of the five constituent symptoms, the percentage of the patients reporting complete remission was bigger with EPs[®] 7630 (**Table 7**). With respect to the percentage of patients reporting complete remission on the individual symptoms of general infection, EPs[®] 7630 showed a significant advantage compared to placebo (**Table 8**).

Table 7 Complete remission on the individual symptoms of bronchitis (Revised table 1 in [21]).

Symptoms	EPs [®] 7630 percentage of patients	Placebo percentage of patients
Cough	51,9%	11.9%
Sputum	68,3%	40.0%
Rales/rhonchi	88,2%	50.0%
Chest pain	93,4%	86.0%
Dyspnoea	87.9%	76.7%

Table 8 Complete remission on the individual symptoms of general infection (Revised 1 in [21]).

Symptoms	EPs [®] 7630 percentage of patients	Placebo percentage of patients
Hoarseness	80.0%	56.4%
Headache	87.8%	68.1%
Fatigue	79.6%	47.2%
Fever	97.5%	91.1%
Limb pain	93.3%	87.6%

In the EPs[®] 7630 group, 84.3% of the patients were very satisfied or satisfied with the treatment compared to 47.7% in the placebo group.

3.2.5 Study 5

“Treatment of acute bronchitis with EPs[®] 7630: Randomized, controlled trial in children and adolescents” [22]:

This randomized, double-blind, placebo-controlled clinical trial was conducted between March and May 2006 in 11 Russian centers by Kamin et al. The purpose of the study was to investigate the efficacy and tolerability of EPs[®] 7630 in children and adolescents suffering from acute bronchitis [22].

The participants (220 male and female patients) aged between 1 and 18 years who met the inclusion criteria were accepted in the clinical trial; categorization criteria included patients with acute bronchitis with bronchitis specific symptoms score (BSS) ≥ 5 points and duration of complaints ≤ 48 hours. In addition, the following are some of the exclusion criteria were used: indication for antibiotic treatment, bronchodilators or glucocorticoids, analgesics other paracetamol, secretolytics, mycolytics or anti-tussiva or other bronchitis medication.

After scrutiny, suitable patients were randomized to 30 drops EPs[®] 7630, 60 drops EPs[®] 7630 or 90 drops EPs[®] 7630, 30 minutes before or after a meal continuously for 7 days, or a matched placebo for the same period.

The primary assessment criterion for evaluating the efficacy variable was the change in the bronchitis specific symptoms (BSS) total score between day 0 and day 7. Bronchitis specific symptoms (BSS) total score was rated on a 5 scale from 0 = (absent) to 4 (very severe). Bronchitis specific symptoms (BSS) total score consisted of the three substantial characteristics associated with acute bronchitis such as coughing, pulmonary rales at auscultation and dyspnea. In both treatment groups, diminished in mean bronchitis specific symptoms (BSS) total score was noticed from day 0 (baseline) to day 7, in the EPs[®] 7630 group, the decrease was 4.4 ± 1.6 points compared to 2.9 ± 1.4 points in the placebo group. In addition, continuous decrease in mean bronchitis specific symptoms (BSS) total score was more noticeable in EPs[®] 7630 group between day 0 and day 7 (**Table 9**).

Table 9 *Continuous decrease in the mean bronchitis specific symptoms (BSS) total score between day 0 (baseline) and day 7 (data collected from [22]).*

Day	EPs [®] 7630 BSS total score	Placebo BSS total score
Day 0	6.0±1.6	5.8± 1.3
Day 3-5	3.6 ±1.4	4.3 ±1.4
Day 7	1.6 ±1.4	2.9 ±1.4

Furthermore, some of the secondary measurement criteria for assessing the efficacy of EPs[®] 7630 were as follows: change in the three response criteria at day seven, treatment outcome, onset of treatment effect and satisfaction with treatment. At day 7, response rate was significantly higher in the EPs[®] 7630 group compared to placebo group in accordance with the three response criteria (**Table 10**).

Table 10 *Response rates in accordance with the three response criteria (data collected from [22]).*

Criterion	EPs [®] 7630 Response Rate	Placebo Response Rate
Criterion 1 BSS total score < 3 points at day 7	81.1%	37.6%
Criterion 2 Decrease by at least 4 points from day 0 to day 7	73.9%	36.7%
Criterion 3 Combination of criteria 1 and 2	64.9%	24.8%

Regarding the individual symptoms coughing and pulmonary rales at auscultation, the mean diminish in bronchitis specific symptoms (BSS) between day 0 and day 7 was more noticeable in the EPs[®] 7630 group compared to placebo group. However, the EPs[®] 7630 demonstrated a non – significant advantage in dyspnea. With regard to general symptoms, lack of appetite was considerably improved in the EPs[®] 7630 group, but with respect to

headache, vomiting and diarrhea there were no significant difference in both treatment groups. Besides, the rate of patients informing onset of treatment effect was significantly higher in the EPs[®] 7630 group compared to placebo group (**Table 11**).

Table 11 *Rate of patients reporting onset of treatment effect (data collected from [22]).*

Day	EPs [®] 7630	Placebo
Between day 1 and 2	19.8%	2.8%
Between day 3 and 4	51.4%	30.3%

Moreover, the percentages of patients on bed rest reduced in both treatment groups (**Table 12**). The treatment outcome was considerably higher in the EPs[®] 7630 group according to Integrative Medicine Outcomes Scale (IMOS). According to integrative medicine patient satisfaction scale at day seven (IMPSS), patients in the EPs[®] 7630 group were more satisfied with the treatment compared to placebo group.

Table 12 *Percentage of patients on bed rest between day 0 and day 7 (data collected from [22]).*

Day	EPs [®] 7630	Placebo
Day 0	17.1%	12.8%
Day 7	0.9%	1.8%

3.2.6 Study 6

“Efficacy and tolerability of EPs7630 tablets in patients with acute bronchitis: a randomized, double-blind, placebo-controlled dose-finding study with a herbal drug preparation from *Pelargonium sidoides*” [23]:

The purpose of this randomised, double-blind, placebo-controlled dose-finding study was to investigate the efficacy and tolerability of EPs[®] 7630 tablets in patients with acute bronchitis [23]. Between February and April 2006 this study was carried out at 16 centres in Ukraine by Matthys et al.

Inclusion criteria were as follows: age >18 years and patients with acute bronchitis with bronchitis specific symptoms score (BSS) \geq 5 points and duration of complaints \leq 48 hours. The participants (total of 406 male and female) patients older than 18 years who met the inclusion criteria were included in the trial.

Furthermore, the following are some of the exclusion criteria applied in the study: evidence for antibiotic treatment, ACE-inhibitors, beta-blockers, bronchodilators or glucocorticoids during the past four weeks before inclusion in the trial, et cetera [23].

After randomization, eligible patients were randomly assigned to receive placebo or 30 mg, 60 mg or 90 mg EPs[®] 7630 three times daily for a period of 7 days. Patients were also allowed to take 500 mg paracetamol if fever equal to or over 39 degrees Celsius occurs during the trial.

The primary measurement criterion for assessing the efficacy variable was the alteration in the bronchitis specific symptoms (BSS) total score between day 0 and day 7. Bronchitis specific symptoms (BSS) total score comprised of the five most substantial features connected with acute bronchitis such as coughing, pulmonary rales at auscultation, chest pain during coughing, sputum, and dyspnea. Bronchitis specific symptoms (BSS) total score was rated on a 5 scale from 0 = (absent) to 4 (very severe). Between day 0 and day 7, it was noticed that the bronchitis specific symptoms (BSS) total score diminished in both treatment groups (Table 13).

Table 13 *Decrease in the bronchitis specific symptoms (BSS) total score between day 0 and day 7 (data collected from [23]).*

30 mg EPs [®] 7630	60 mg EPs [®] 7630	90 mg EPs [®] 7630	Placebo
4.3 ± 1.9	6.1 ± 2.1	6.3 ± 2.0	2.7 ± 2.3

In addition, some of the secondary assessment criteria for evaluating the efficacy of EPs[®] 7630 compared with placebo were as follows: alteration in the three response criteria at day seven, treatment outcome and onset of treatment effect. Between day 0 and day 7, the response rate was higher in the EPs[®] 7630 groups compared to placebo (Table 14).

Table 14 *Response rate in both treatment groups between day 0 and day 7 according to three criteria (data collected from [23]).*

Criterion	30 mg EPs [®] 7630	60 mg EPs [®] 630	90 mg EPs [®] 7630	Placebo
Criterion 1 BSS total score < 3 points on day 7	24.5%	57.4%	55.0%	5.9%
Criterion 2 Decrease in BSS total score of at least 7 points from 0 to day 7	14.7%	43.6%	46.0%	6.9%
Criterion 3 Combination of criteria 1 and 2	6.9%	33.7%	31.0%	2.9%

Regarding the individual symptoms, the mean decrease in bronchitis specific symptoms (BSS) from day 0 to day 7 was more noticeable in the EPs[®] 7630 groups compared to placebo group. The treatment outcome was significantly higher in the EPs[®]7630 group according to Integrative Medicine Outcomes Scale (IMOS). With respect to satisfaction with treatment, patients in the EPs[®] 7630 were more often satisfied or very satisfied compared to the placebo group (**Table 15**).

Table 15 *Percentage of patients satisfied with the treatment according to IMPSS (data collected from [23]).*

30 mg EPs [®] 7630	60 mg EPs [®] 7630	90 mg EPs [®] 7630	Placebo
55.9%	86.2%	84%	23.5%

3.3 Interactions

3.3.1 Koch et al [24]:

The primary objective of this study was to investigate the impact of Pelargonium sidoides extract EPs[®] 7630 on blood coagulation or on the pharmacokinetics of warfarin. The study was performed by Koch et al.

The duration of the experiment was 2 weeks and the test animals were male Sprague-Dawley rats. The test animals were given three different doses of EPs[®] 7630 (10, 75, 500mg/kg). In

addition, the following assays were conducted: thromboplastin time/quick test (TPT), partial thromboplastin time (PTPT) and thrombin time (TT).

With respect to effect of EPs[®] 7630 on coagulation parameters, there was no evidence of alteration in coagulation parameters according to the values of partial thromboplastin time (PTPT) and thrombin time (TT). However, compared to the control group, the thromboplastin time/quick test (TPT) in animals treated with 10 or 500mg/kg of EPs[®] 7630 was to some extent shortened (**Table 16**).

Table 16 *Effect of 2 weeks oral treatment with EPs[®] 7630 on (TPT), (PTPT) and (TT) in rats, including Means±SD. (Revised table 2 in [24]).*

	EPs [®] 7630 10mg/kg	EPs [®] 7630 75mg/kg	EPs [®] 7630 500mg/kg	Control group
No. of animals	10	10	10	10
TPT (s)	9.21±0.22	9.51±0.39	9.28±0.24	9.55±0.35
PTPT (s)	28.73±2.98	27.77±3.08	28.81±5.38	28.05±3.93
TT (s)	62.94±6.51	61.67±4.85	62.91±4.10	62.63±3.59

Regarding effect of the combination of EPs[®] 7630 and warfarin on coagulation parameters, there was no influence of EPs[®] 7630 on the blood coagulation in the experiment performed. In respect of effect of EPs[®] 7630 on the pharmacokinetics of warfarin, there was no statistically different in warfarin plasma levels between EPs[®] 7630 group and control group (**Table 17**).

Table 17 *Effect of 2 weeks oral treatment with EPs[®] 7630 (500mg/kg) or vehicle (agar suspension, 0, 2 %, 10ml/kg) on the pharmacokinetic parameters of warfarin (0,2mg/ p.o.) in rats. (Revised table 4 in [24]).*

Test group	Cmax (ng/ml)	Tmax (h)	AUC (0-t) (ng/ml h)	AUC (0- infinty) (ng/ml h)	t1/2 (h)
EPs7630	945	8	35,321	43,533	36
Control group	1096	8	32,938	41,831	37

3.4 Adverse events

With respect to adverse events, 2 of 52 patients (3.8%) in the EPs[®] 7630 and 1 of 51 patients (2.0%) in placebo group experienced adverse events in study 1. But none of these adverse events was assessed as serious. Additionally, in two patients, the adverse event was considered as unrelated to the study drug (moderate tracheitis in one patient in EPs[®] 7630 group and severe tracheitis in one patient in placebo group) [18]. A causal relationship to the study could not be excluded in one patient in the EPs[®] 7630 group (mild epistaxis) [18].

Furthermore, in study 2, 15 of 64 patients (23.4%) in the EPs[®] 7630 and 10 of 60 patients (16.7%) in the placebo group perceived adverse events during the trial. But none of these adverse events was mentioned, all adverse events were evaluated as non-serious.

Gastrointestinal disorders were the most frequent adverse events experienced by the participants in Study 3 (**Table 18**). However, none of these adverse events was assessed as serious.

Table 18 Adverse events experienced by the participants in study 3 (data collected from [20]).

Adverse event	30 mg EPs [®] 7630	60 mg EPs [®] 7630	90 mg EPs [®] 7630	Placebo
Gastrointestinal disorder	22.8%	17.2%	19.2%	17.8%

In addition, adverse events were observed in both treatment groups in study 4, 23 of 108 patients (21.3%) in the EPs[®] 7630 group and 24 of 109 (22%) in the placebo group. An increase in the erythrocyte sedimentation rate and changes in leucocyte count were observed which were due to the underlying infectious disease (**Table 19 - 20**) [21]. Nonetheless, all adverse events were assessed as non-serious.

Table 19 Increase in the erythrocyte sedimentation rate (data collected from [21]).

Erythrocyte	EPs [®] 7630 Number of patients/%	Placebo Number of patients/%
Erythrocyte	10 of 108 (9.3%)	10 of 109 (9.2%)

Table 20 Changes in leucocyte count (data collected from [21]).

Leucocyte	EPs [®] 7630 Number of patients/%	Placebo Number of patients/%
Leucocyte	4 of 108 (3.7%)	5 of 109 (4.6%)

Moreover, three adverse events were noticed in 2 of 111 patients in the EPs[®] 7630 group in study 5. Three adverse events were noticed in two of 111 participants in the EPs[®] 7630 group. A causal relationship of the adverse events with the investigational medication was excluded in all three cases [22]. But, all adverse events were evaluated as non-serious.

In study 6, the adverse events reported were gastrointestinal disorders (**Table 21**). Nevertheless, none of these adverse events was assessed as serious.

Table 21 Adverse events experienced by the participants in study 6 (data collected from [23]).

Adverse event	30 mg EPs [®] 7630 Number of patients/%	60 mg EPs [®] 7630 Number of patients/%	90 mg EPs [®] 7630 Number of patients/%	Placebo Number of patients/%
Gastrointestinal disorder	5 of 102 (4.9%)	9 of 101 (8.9%)	15 of 101 (14.9%)	6 of 102 (5.9%)

de Boer et al [6].

The six clinical studies used in the clinical section of this literature study mentioned only a few of the adverse events experienced by the participants. Nonetheless, in Germany, 34 cases of allergic reactions suspected to be affiliated with the use of extract from the roots of Pelargonium were declared and two of patients that experienced allergic reactions needed treatment for circulatory failure [6]. The following are some of the allergic reactions reported; asthma, skin rash with itching, urticarial, dermatitis, pruritus, conjunctivitis, rhinitis, swelling of the lips and tongue [6].

4. Discussion

As stated earlier, the purpose of this degree project is to carry out a literature study in order to answer the following questions: Is *Pelargonium sidoides* effective against viruses or bacteria that cause respiratory tract infection? Are there clinical significant effects of extract (EPs[®] 7630)? Are there interactions associated with extract (EPs[®] 7630)? Are there adverse events associated with extract (EPs[®] 7630)?

Study Design

The six studies in the clinical evidence section of this literature study were relatively large i.e., the number of participants in each study group were high, at least in the context of natural drugs (103 participants in the smallest study group and 406 participants in the largest study group), large studies may provide more accurate results. In addition, all the six studies were multicenter, prospective, randomized, double-blind, placebo-controlled clinical studies. These kind of studies (randomized, double-blind) are regarded as effective and can reduce systematic error (bias). The inclusion and exclusion criteria in all the studies were very pronounced, which also reduce bias. Request for a written consent from the participants before the starting day of studies, also contribute to good quality of studies. The eligible participants received randomized treatment (EPs[®] 7630 or placebo) for a period of 7 to 10 days, which corresponds to the normal duration of common cold or acute bronchitis.

In vitro studies (bacteria and viruses)

In the study conducted by Conrad et al. extract EPs[®] 7630 (doses between 0 and 30 microgram/ml) was tested on streptococcus pyogenes and examined by flow cytometric assay. The study showed that extract EPs[®] 7630 reduced bacterial adhesion to invading host epithelial cells and also increased the attachment of bacteria to decaying BEC which may lead to inactivation and trap of pathogens. In addition, the study showed that extract EPs[®] 7630 inhibited A-streptococci (GAS) invasion of epithelial cells.

In the study performed by Michaelis et al. effect of *Pelargonium sidoides* extract EPs[®] 7630 on replication of a panel of respiratory viruses was investigated. Extract EPs[®] 7630 with concentration up to 100 microgram/ml was tested in cells infected with respiratory viruses. Cell viability assay and cytopathogenic effect (CPE) reduction assay were conducted. The study showed that extract EPs[®] 7630 at a concentration of 100 microgram/ml inhibited the replication of respiratory viruses (e.g., H1N1 influenza, H3N2 influenza, respiratory syncytial virus (RSV), coronavirus (HCoV-229E), parainfluenza virus 3 and coxsackie virus A9).

Viruses or bacteria are believed to be the cause of respiratory tract infection. Since adhesion to the cell surface is the first stage in infection and plays a great role in the interaction between pathogens and host epithelia, therefore based on the finding in the above studies, extract EPs[®] 7630 appears to have multiple effects which may be advantageous in respiratory tract infection.

Common cold

Study 1 is the only study among the six studies used in the clinical evidence section of this literature study that dealt with common cold. In this multicenter, prospective, randomized, double-blind, placebo-controlled clinical study carried out by Lizogub et al. participants were treated with 30 drops (1.5 mL) of EPs[®] 7630 or placebo for 10 days, the study showed that EPs[®] 7630 was more effective compared to placebo i.e., the duration of incapability to work was shortened by 1.5 days in the EPs[®]7630 group.

Since common cold is one of the most common health complaints for which people seek primary care and one of the reasons for absenteeism from work and school, if extract EPs[®] 7630 reduces inability to work or attend school by 1.5 day then it will save a lot of money for the individuals, employers and the government. But common cold symptoms vary individually, the symptoms may be mild or severe, in most cases it goes away by itself without medication and the worst period is the first few days. The individual duration of Study 1 was 10 days which was relatively short. How can we be sure that the recovery rate was directly dependent on the effect of the investigational medication?

However, based on the finding from this study EPs[®] 7630 appears to be effective in treatment of common cold.

Acute Bronchitis

Study 2 – study 6 in the clinical evidence section of this literature study are studies that dealt with acute bronchitis. Study 3 and study 6 were conducted as dose-finding with 4 parallel treatment groups with individual duration of 7 days. The studies showed that 60 mg and 90 mg EPs[®] 7630 were more effective compared to placebo i.e., duration of inability to attend kindergarten, school or work was shortened in the EPs[®] 7630 groups. In study 2 and study 4, participants received randomized treatment for 7 days, 30 drops (1.5 mL) of EPs[®] 7630 or placebo. The results of both studies showed that EPs[®] 7630 were more effective compared to placebo.

In most cases acute bronchitis goes away by itself within one to two weeks without medication, sometimes the symptom of acute bronchitis (e.g., cough) can last for another couple of weeks [24]. Since acute bronchitis is one of the most common reasons for which people seek medical care, if extract EPs[®] 7630 reduces inability to attend kindergarten, school or work then it will be beneficial for the individuals, employers and the government economically. EPs[®] 7630 appears to be effective in treatment of acute bronchitis based on the results of the five studies.

Interactions

The study conducted by Koch et al. shows no pharmacokinetic or pharmacodynamics interactions between Pelargonium sidoides extract (EPs[®] 7630) and warfarin. With respect to effect of the combination of EPs760 and warfarin on coagulation parameters, no significant influence was noticed compared to animals which were only treated with warfarin [24]. But, it is stated in the information leaflet of Kaloba “you should not use Kaloba tablets if you have a tendency to bleed and / or are taking blood-thinning medication without discussing it with your doctor”.

The use of herbal remedies can provide interaction with other drugs, which are often overlooked by users. It has been suspected that medicinal herbs, if exerting a clinical effect, may also interact with concurrently used pharmaceutical medicines [25]. Diseases requiring treatment with drugs with narrow therapeutic windows that are sensitive to changes in concentration and external influences for optimal effect and overdose symptoms are clear risk factors for interactions with herbal remedies [2].

Since there are biological differences between species, animal tests cannot definitely foresee all outcomes in humans, so there must be a little difference in the results of studies with rats or humans respectively.

Adverse events

In respect of adverse events, all the six studies in the clinical section of this literature study declared that some of the participants experienced adverse events during the trials and were evaluated as non-serious, but not all the adverse events were mentioned. Allergic reactions can be elicited by any drug, and idiosyncratic response by definition cannot be foreseen; these are certainly not restricted to plant medicines, although some plant families are notorious for their allergenicity [25]. Herbal drugs usually contain substances with antigenic properties (e.g. terpenes, coumarins, proteins or glycosides) [6].

In the study performed by de Boer et al. allergic reactions suspected to be affiliated with the use of extract from the roots of Pelargonium were reported [6]. As with all medicines, side effects and interactions with other drugs are possible; but these are a consequence of the therapeutic use of the herb and an assessment of the usual risk: benefit ratio should be made [25].

Nonetheless, it is stated in the information leaflet of Kaloba “Stop taking Kaloba tablets and contact your doctor immediately if you experience swelling of the face, tongue and / or throat, shortness of breath or difficulty swallowing. Stop taking Kaloba tablets if you develop a rash”.

5. Conclusion

Pelargonium sidoides extract EPs[®] 7630 appears to be an effective treatment for respiratory tract infection based on the findings in this literature study. Gastrointestinal disorders and allergic reactions are the most frequent adverse events associated with extract EPs[®] 7630.

The results of the study of interactions between EPs[®] 7630 and warfarin has not sufficiently strong evidence, more studies need to be performed in order to draw a conclusion.

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Appendix

- The method used to count and examine microscopic particles is called flow cytometry [26].
- The process used to examine bleeding disorders and to observe patients taking an anticoagulating drug is known as partial thromboplastin time (PTT) [27].
- The test used to determine the time taken for a plasma sample to clot on addition of thrombin is called thrombin time (TT) [28].
- Blood test used to examine inflammation or abnormal proteins in the body is known as erythrocyte sedimentation rate [29].
- Blood test used to find out the number of white blood cells is called leukocytes count or WBC count [30].
- Cytopathic effect is every detectable change in the host cell as the result of infection [31].
- Cell viability is a process used to determine living or dead cells, based on a total cell sample [32].



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