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# Fifatrol, An Ayurvedic Formulation- A Prospective Multi-Center Observational Study On The Symptoms of Upper Respiratory Tract Infections

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## ABSTRACT: -

**Background:** Upper respiratory tract infections (URTI) is a leading cause of economic burden as it remains among the top 3 diagnosed diseases globally with an estimated annual cost above $22 billion. Available medications to treat URTI and associated symptoms are effective, however, their tolerability remains a challenge for the practitioners. Recently, the use of alternative and complementary therapy has increased for the management of URTI symptoms. Fifatrol is an ayurvedic formulation for the management of URTI and its associated symptoms. However, its evidence-based data is limited. Therefore, this observational study was aimed to investigate the effects and to assess the safety of Fifatrol on URTI symptoms.

**Method:** A post-marketing prospective observational study was carried out in the various cities of India. Patients enrolled in the study were presented with the symptoms of URTI in the health care centers and prescribed Fifatrol in twice-daily dose by the practitioners voluntarily. Symptoms of URTI (local, general, total) were collected on a 0–7 Likert scale at three-time points within 1 week (1st day, 4th day, and 7th day), using a questionnaire. Effectiveness was evaluated by examining the reduction in symptoms scores at day 4 and 7 respectively from baseline (day 1)

**Results:** The mean score of local symptoms was 19.49 (SE: 0.39) on the day 1, dropping to 6.82 (SE: 0.14) and 1.84 (SE: 0.04), showing a decrease of 65.0% and 90.55% on the 4th and 7th day respectively ($p < 0.001$). The mean score of general symptoms reduced from 8.06 (SE: 0.26) on day 1 to 1.62 (SE: 0.5) and 0.8 (SE: 0.03), revealing a reduction of 79.9% and 90.11% on the 4th and 7th day respectively ($p < 0.001$). The mean total score of symptoms reduced from 28.34 (SE: 0.59) on day 1 to 8.63 (SE: 0.15) and 2.73 (SE: 0.05), indicating a decrease by 69.5% and by 90.36% on the 4th and 7th day respectively ($p < 0.001$). 1.97% adverse events of mild intensity reported during the observation period.

**Conclusions:** This observational study has gathered evidence about the effectiveness and safety of Fifatrol on the amelioration of the symptoms of URTI.

**Keywords:** URTI, Fifatrol, Polyherbal formulation, Post-marketing observational study

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## INTRODUCTION

Upper respiratory tract infections (URTI) including acute bronchitis, the common cold, influenza, and respiratory distress syndromes can be caused by a variety of viruses and bacteria. URTI can be described as cough-associated irritation and inflammation in the upper part of the airways with no evidence of pneumonia and no history of emphysema/COPD/chronic bronchitis. The organs involved in the URTI are the nostrils, sinuses, pharynx, larynx, and airways[1].

In the outpatient setting, URTI is a leading cause of economic burden and remains among the top 3 diagnosed diseases and estimated an annual cost above $22 billion excluding costs related to influenza [2]. URTI accounts for around 10 million outpatient consultations in a year especially because of the severity of its symptoms. The estimated yearly frequency of URTI symptoms including common cold in adults and pediatrics are 2-3 and up to 8 respectively [3-6].

The first objective of treatment for the URTI remains relief from the symptoms. Antibiotics, antivirals, decongestants, H1-receptor antagonists, etc are the available medications for URTI [7]. However, evidence-based information doesn't uphold the use of antibiotics as a treatment and management of the common cold since antibiotics do not alleviate symptoms or the course of disease [3,8]. As per a Cochrane Review, the prophylactic utilization of vitamin C at a dose of 200 milligrams/day or above had a "modest yet steady impact" on the term and seriousness over the symptoms of common cold [9]. Additionally, the tolerability of these medications remains a challenge for practitioners. Recently, the use of alternative and complementary therapy has increased for the management of URTI symptoms [9]. Fifatrol has been well accepted by the physicians of Ayurveda for the successful management of conditions like Flu & URTI and symptoms like fever, nasal congestion, running nose, etc. Fifatrol is a rich combination of Five vital classical formulations like *Tribhuvan Kirti Rasa*, *Mrtunjay Rasa*, *Sanjivani Vati*, *Sudershan Ghan Vati & Godanti Bhasam* from the ancient texts of Ayurveda fortified with extractives from eight prominent herbs like *Guduchi* (*Tinospora cardifolia*), *Daruharidra* (*Berberis aristata*), *Chirayata* (*Swertia chirata*), *Kutaki*( *Picrorhiza Kurroa*) Tulsi (*Ocimum sanctum*), *Apamarga* (*Achyranthes aspera*), *Karanja* (*Pongamia pinnata*), *Motha* (*Cyperus rotandus*) which are well documented for their potent antibacterial and anti-viral actions along with immuno-modulatory, antipyretic, analgesic, and antihistaminic effects [10]. It improves the immune system to fight against viruses & other infections eases the associated symptoms and fastens the recovery. It helps fast relief from nasal congestion, body ache, sore throat, and headache [11]. However, the supportive evidence to claim these benefits with Fifatrol is limited. Therefore, this observational study was

aimed to investigate the effects and to assess the safety of the Fifatrol on URTI symptoms, through a questionnaire-based examination of patients.

## METHOD

### Study Design

A post-marketing prospective observational study was carried out in the various cities of India (from December 2019 to April 2020). Twenty-two community-based primary health care centers were previously selected as the recruitment sites. The most physician involved in this study were general physicians and previously prescribing Fifatrol in the management of URTI.

### Study Population

Patients enrolled in the study were presented with the symptoms of URTI in the health care centers and prescribed Fifatrol by the practitioners voluntarily. Inclusion criteria were set if the patient was confirmed with URTI either by positive pathological report or discretion of the practitioner and being prescribed Fifatrol monotherapy. Further inclusion criteria were: age > 18 years, presence of fever in last 48 hours, presence of at least one symptom: headache, throat, cough, nasal discharge sore or ingestion, muscle pain, sweating, and fatigue. Exclusion criteria were: Absence of URTI and fever, presence of pregnancy, and malignancy.

The primary endpoint was set to evaluate the cessation of symptoms within the follow-up of 7 days. The sample size was calculated as 188 (minimum) to detect statistical significance at 90% power with a standard deviation of ± 1.23 assuming a probability of 5% type 1 error.

### Data collection

Eligible patients were invited to voluntarily fill pre-approved informed consent form. After that Practitioners finished a questionnaire (supplementary document 1: Questionnaire.doc). Symptoms were collected on day 1 of the visit at the health care center and followed up on day 4 and day 7. Patient symptoms were classified as local symptoms and general symptoms (Table 1).

**Table 1: Classification of symptoms**

| Local Symptoms | General Symptoms |
|---|---|
| Cough | Fatigue |
| Itchy Throat | Body Pain |
| Sneezing | Rigors |
| Nasal Congestion | |
| Sore Throat | |
| Hoarseness | |
| Headache | |

A Likert scale of 0-7 was used and symptoms were scored, denoting 0 as the absence of symptom and 7 as maximal severity respectively. Three indexes were calculated for each patient, local symptoms score, general symptoms score, and total symptoms score. The total symptoms score was the sum of the local symptoms score and general symptoms score [25].

Patient clinical characteristics and socio-demographic were collected prospectively including gender (male/female), age (years), BMI(Kg/m2), smoking (Yes/No), and presence of chronic conditions (yes/no). Patients receiving any other treatment of chronic illness and URTI were also collected.

**Primary endpoints**

The primary endpoint was the reduction in the severity of the URTI symptoms from day 1 to the study follow-up period i.e., on day 4 and day 7.

**Secondary endpoints**

The secondary endpoints were to assess the safety of the Fifatrol.

**Compliance and adverse events**

Patients were asked to report compliance with Fifatrol usage as directed by the practitioner at each follow-up visit. All Adverse events occurring during the study were recorded and their relationship to the study medication was determined.

**Statistical analysis:**-Data were summarized using descriptive statistics as mean, and standard error. Pearson's $\chi 2$ tests were performed for comparisons between categorical variables. For the comparisons of paired differences, McNemar tests and Paired Samples T-test were used. For statistical significance, a p-value of $< 0.05$ was considered. Statistical software used were IBM SPSS version 22.0 and Graph Pad Prism 8.0 software (USA).

## RESULTS

**Study Population**

Twenty-two primary health care centers in various cities in India recruited patients for this study. Initially, 339 patients were screened for primary investigation. 112 patients were excluded as they did not meet the inclusion criteria. A total of 227 patients were recruited and 203 (89.4%) were included in the final analysis. Twenty-four patients were concluded by the practitioners to be "not evaluable", as they missed the follow-up (Figure 1).

**Baseline characteristics**

The patient's mean age was 39.43 (S.E. 0.72) years, while 109 (54%) were males. Mean BMI was 26.76 (S.E. 0.30) kg/m2,49 (24%) reported at least one chronic condition at backgrounds such as diabetes mellitus and hypertension and 56 (28%) patients were current smokers (Table 2).

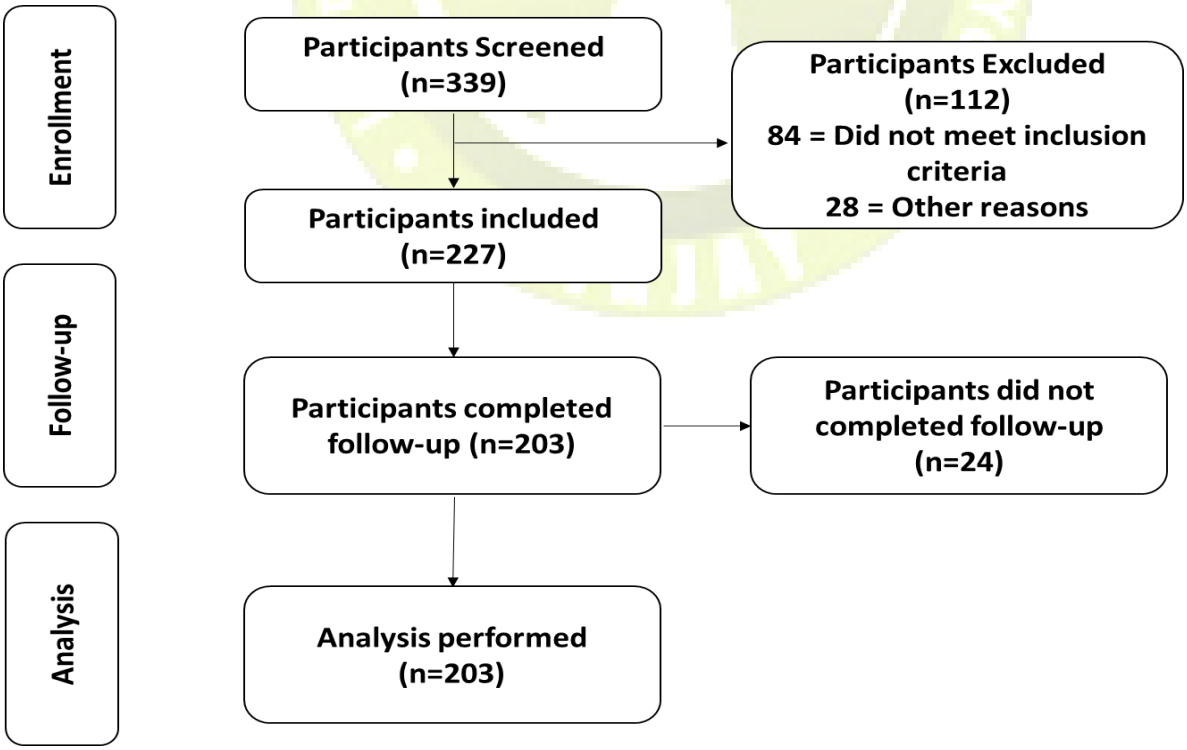



**Figure 1: Flowchart of the patients included and analyzed in the study**

**Table 2: Characteristics of the patients**

| Patients Characteristics (n=203) | | | |
|---|---|---|---|
| | **Mean ± S.E.** | **Minimum** | **Maximum** |
| **Male** | **109 (54%)** | | |
| **Female** | **94 (46%)** | | |
| **Age** | **39.43 ± 0.72** | **21** | **68** |
| **Weight (Kg)** | **67.89 ± 0.83** | **46.36** | **106.21** |
| **Height (m)** | **1.59 ± 0.03** | **1.36** | **1.79** |
| **BMI (kg/m2)** | **26.76 ± 0.30** | **19.88** | **36.29** |
| **Smoker** | **56 (28%)** | | |
| **Chronic Illness** | **49 (24%)** | | |

**Primary endpoint: Changes in the severity of the symptoms from baseline (Day 1)**

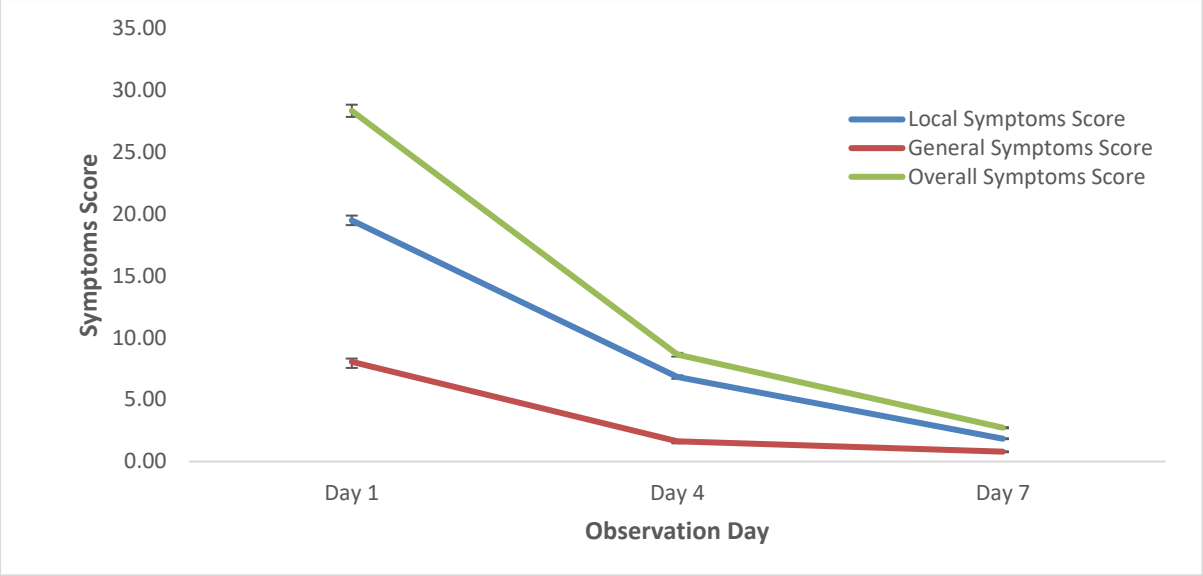
Table 3 represents the Mean ± SE scores of local, general, and the total (local plus general) score of symptoms during the study period, along with the changes in individual means of scores of symptoms from baseline (day 1) to different follow-up days (day 4 and day 7). The mean score of Local symptoms was 19.49 ± 0.39 on day 1, dropping to 6.82 ± 0.14 and 1.84 ± 0.04, showed a decrease of 65.0% and 90.55% on the 4$^{th}$ and 7$^{th}$ day respectively ($p < 0.001$). The mean score of general symptoms reduced from 8.06 ± 0.26 on day 1 to 1.62 ± 0.5 and 0.8 ± 0.03, showing a reduction of 79.9% and by 90.11% on 4$^{th}$ and 7$^{th}$ day respectively ($p < 0.001$). The mean total score of symptoms declined from 28.34 ± 0.59 on day 1 to 8.63 ± 0.15 and 2.73 ± 0.05, indicating a decrease by 69.5% and by 90.36% on 4$^{th}$ and 7$^{th}$ day respectively ($p < 0.001$). On the first day, 203 patients reported having fever. This rate dropped to 7.0% on day 4 and to 1.89% on day 7 ($p < 0.0001$ for paired differences) (Figure 2).

**Table 3: Changes in the severity of the symptoms from baseline**

| **Days of Observation** | **Local Symptoms Score** | | **General Symptoms Score** | | **Total Symptoms Score** | |
|---|---|---|---|---|---|---|
| | Mean | S. E. | Mean | S. E. | Mean | S. E. |
| **Day 1** | 19.49 | 0.38 | 8.06 | 0.26 | 28.34 | 0.50 |
| **Day 4** | 6.82 *** | 0.14 | 1.62 *** | 0.05 | 8.63 *** | 0.15 |
| **Day 7** | 1.84 *** | 0.04 | 0.8 *** | 0.03 | 2.73 *** | 0.05 |
| Reduction in Mean Symptoms Score (Day 1-7) | 17.65 | 0.34 | 7.26 | 0.23 | 25.61 | 0.45 |

Data is presented as Mean and standard error (S.E.). Local symptoms (cough, itchy throat, sore throat hoarseness, sneezing, nasal congestion, and headache); General symptoms (fatigue, body pain, and rigors); Overall symptoms (Sum of local Symptoms and general Symptoms).

**Figure 2: Changes in the severity of the symptoms from baseline**




Data is presented as Mean and standard error (S.E.). Local symptoms (cough, itchy throat, sore throat hoarseness, sneezing, nasal congestion, and headache); General symptoms (fatigue, body pain, and rigors); Overall symptoms (Sum of local Symptoms and general Symptoms).

**Secondary endpoint: Compliance and Adverse events**

Adherence to the therapy was high in patients throughout the study. 94.58% and 83.74% of patients reported complete compliance as directed by practitioners on day 4 and day 7 respectively. There were 4 (1.97%) adverse events reported during the observation period. All reported adverse events were mild and did not cause the withdrawal of therapy. 2 patients (0.99%) reported mild gastric disturbance and the rest 2 (0.99%) patients reported dryness of the mouth (Table 4). Among all 4 adverse events, 3 (1.48%) were reported in patients with chronic illness, who were taking co-medication in the background. 1 (0.49%) patient receiving monotherapy reported mild gastric discomfort.

**Table 4: Adverse events in the observation period**

| ADR (n=4) | Severity |
|---|---|
| Gastric Disturbance (n=2) | Mild |
| Dryness of mouth (n=2) | Mild |

## DISCUSSION

The present study was aimed to evaluate the effectiveness of the combination of Ayurvedic herbs, Fifatrol on the amelioration of the symptoms of URTI. Results of the present study suggest that the Fifatrol treatment for 7 days could alleviate the local symptoms (65.0% on day 4 and by 90.55% on day 7), the general symptoms (79.9% on day 4 and by 90.11% on day 7) and the overall symptoms (69.5% on day 4 and by 90.36% on day 7) of URTI. Moreover, fever among the patients was declined to 7.0% on day 4 and to 1.89% on day 7 with the Fifatrol treatment.

Polyherbal formulations are widely accepted for the management of various diseases because of their multiple ingredients, which, by acting on various underlying pathological mechanisms and alleviates disease progression. Fifatrol is also such formulation that contains

five classical Ayurvedic formulations which are fortified with extracts from prominent herbs such as Guduchi, Karanj, Apamarg, Tulsi, Kutaki, and others that have been well known for their immunomodulatory effect as well as potent antibacterial and antiviral action [10]. In a preliminary study, Fifatrol extract was found effective against *Pseudomonas aeruginosa*, *Salmonella typhi, and Staphylococcus spp*. at 1mg/ml concentration in another *in-vitro* study. Recently, an ayurvedic regimen including Fifatrol was found effective in offering symptomatic relief (fever, dyspnea, anorexia, fatigue, anosmia, and dysgeusia) in mild to moderate cases of coronavirus disease-19 (Covid-19). After the treatment, fever, sore throat, breathlessness, anorexia, and cough were completely subsided with remarkable relief in body ache, headache, and fatigue along with all symptoms like taste and smell loss also reversed [11]. The composition of Fifatrol is effective against infectious diseases and their symptoms *viz* URTI, typhoid, malaria, etc. Previous studies have reported that *Tribhuvan Kirti Rasa, Godanti Bhasma,* and *Sudarshan Ghana Vati*, classical herbs-mineral formulations and composition of Fifatrol are safe and therapeutically effective in a wide range of disease and their symptoms especially jwara (fever) [12-13].

Fever also referred to as pyrexia, can be caused by many pathological conditions mainly caused by viral, bacterial, and parasitic infections that result in influenza, the common cold, urinary tract infections, URTI, Covid-19, and malaria [14]. One of the therapeutic approaches to treat infections includes controlling the elevated temperature of the body. In the present study, all the patients with URTI were presented with fever which is in line with previous evidence, however, after treatment with Fifatrol the fever was significantly dropped to 7.0% on day 4 and to 1.89% on day 7. This antipyretic action of Fifatrol might be due to the presence of classical preparation *Godanti Bhasam* as WHO recommended its usage for common cold and fever in traditional medicine in Asia [15]. *Godanti Bhasam* is reported to provide antipyretic action by influencing the thermo-sensitivity of neurons & dilating the cutaneous blood vessels [15]. Additionally, *Godanti Bhasam* can improve strength and phagocytic activity by promoting the maturation of macrophages [16]. In a clinical study conducted on 593 patients of different age and severity, *Godanti Bhasam* (Gypsum) at a dose of 1-3 gm twice daily relived joints and muscular pain in fever by showing analgesic effect. Gypsum also remarkably relieved muscular pain, improved articular flexibility, and reduced muscular rigidity [17]. In an *in-vitro* study, *Mrityunjaya Rasa* showed anti-microbial potential against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa,* and *Salmonella typhi* [18].

*Tinospora cordifolia* is reported to possess antipyretic, antidiabetic, antispasmodic, hepato-protective, anti-inflammatory, antioxidant, anti-allergic, anti-stress, antimalarial, immunomodulatory activities [19]. *Swertia chirata* is reported to offer anti-inflammatory, hepatoprotective, antibacterial, antioxidant, antiulcer, antimalarial, and antipyretic potential [20]. Navjeet Singh et al have summarized the beneficial effects of *Achyranthes aspera* as an antiallergic, nephroprotective, antiparasitic, analgesic, antipyretic and suggested that it can be used in the treatment of many diseases *viz* cold, cough, ear complications, bronchitis, and headache [21]. Furthermore, as per experimental and clinical studies, *Berberis aristata* exerts various pharmacological effects like anti-microbial, antihistaminic, antipyretic, hepatoprotective and antidiabetic, and cardioprotective activities [22]. Additionally, *Picrorhiza kurroa* is reported widely for its potential against URTI, fever, and dyspepsia [23]. In the present study also,

treatment with Fifatrol showed significant relief in the symptoms of URTI such as cough, itchy throat, sore throat hoarseness, sneezing, nasal congestion, headache, fatigue, body pain, and rigors. This result might be due to the synergistic effects of classical preparations and herbal extracts present in Fifatrol [21-23].

Ayurvedic formulations are considered to be safe and durable, however, regulatory authorities suggest that herbal medicinal products (HMP) should be free from impurities and to have safety data in animals as well as in humans [24]. To comply with the guidelines of regulatory authorities on HMP, we performed quality and toxicities studies. In our preliminary studies, Fifatrol was found free from any impurities as well as did show any sign of toxicity up to 1240 mg/kg in Wistar rats following OECD guidelines for repeated dose 28 days oral toxicity study. Furthermore, in the present study, only four patients (1.97%) reported adverse events of mild intensity (2 cases each of gastric disturbance and dryness of the mouth) and did not cause the drug withdrawal. Among all these events three were reported in the patients with co-morbidities and were already taking supportive therapies.

The present study is inclined to some limitations considering its observational design, including the way that there was no control group for similar outcomes. Moreover, data about the day-to-day course of treatment of patients couldn't be collected, since the information was taken at two different time points of follow-up (on day 4 and day 7). The presence of fever in exact temperature was not recorded but recorded as a dichotomous variable (no/yes). Moreover, it was impractical to decide the treatment effect on explicit viral diseases, since there was no identification measured of strains and burden of the virus. Further, the safety of the treatment was observed for 7 days observational period only that makes difficult to find out the causal relationship with adverse event. Therefore, further studies are warranted to explicate these benefits in randomized clinical settings.

## CONCLUSIONS

This study presented preliminary evidence of the potential safety and effectiveness of Fifatrol in the management of the symptoms of URTI. The regression in the symptoms might be attributed to the anti-viral, anti-bacterial, antipyretic, analgesic, antihistaminic, anti-inflammatory, antioxidant, immunomodulatory effects synergistically of the herbo-mineral composition of Fifatrol.

### Acknowledgment

The authors of this study are thankful to the Physicians for providing the required details during the observation period.

### Abbreviations

URTI: Upper respiratory tract infections: HMP: herbal medicinal products; WHO: World Health Organisation; OECD: Organisation for Economic Co-operation and Development

### Conflict of Interest

The authors of the study declare no conflict of interest

### Availability of data and materials

The Supplementary datasets used or/and analyzed in the present study can be made available from the corresponding author on reasonable request.

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