

# The evaluation of efficacy and safety of Cough (EMA) granules used for upper respiratory disorders

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**Abstract:** Ivy leaf is used for the treatment of respiratory diseases with the intensive mucus formation, respiratory infections, and irritating cough coming from the common cold. Conferring to clinical trials, the efficacy, and tolerability of ivy leaf is good. The main compounds accountable for biological activity are triterpene and saponins. Ivy leaves show convulsive/antispasmodic, anti-inflammatory, antimicrobial, analgesic, anthelmintic and anti-thrombin activity. Not only ivy but also marshmallow and mustard seeds are used for these indications. This study was conducted to evaluate the efficacy and safety of Cough (EMA; European Medicines Agency) granules used for upper respiratory disorders. This clinical trial was conducted on 150 patients, out of which 75 received the Cough (EMA) granules and 75 received the placebo. The age range of patients was 3 years to above 15 years. The sample paired t-test was applied to evaluate the significant level. Cough (EMA) granules were found effective in the treatment of cough, cold, and flu symptoms. The new treatment Cough (EMA) granules were safe and well tolerated in patient at given specific age group. The study recommends that Cough (EMA) granules can be used effectively in the treatment of upper respiratory tract infection.

**Keywords:** Cough (EMA) granules, herbal treatment, cold and flu.

## INTRODUCTION

The common cold is the most morbid disease in children and adults. According to a report, in the United States of America, approximately 1 billion people suffer from common cold every year (Shah, Sander *et al.*, 2007). Adults have fewer episodes of common cold compared to children. The most common viruses participating to cold symptoms are rhinovirus and coronavirus, other than that approximately 200 more viruses have been identified that can cause the symptoms of common cold (Makelä, Puhakka *et al.*, 1998). The common cold is concomitant with a large economic burden on the society (Close). *Hedera helix* (L.) (Ivy leaf) is a perennial plant belongs to family Araliaceae. It is the main natural prescription containing saponin, which is essentially utilized as a part of monotherapy due to expectorant and broncho-spasmolytic impacts (Green, Ramsey *et al.*, 2011). Various controlled clinical studies demonstrated their individual helpful adequacy utilizing a dry concentrate of ivy leaves for human utilization from a watery ethanolic

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separate (extraction medium: 30% ethanol, Drug extricate Ratio (RSD) 5-7, 5: 1); (Lassig *et al.*, 1996; (Efeublättertrocken extract, 1997); (Mansfeld, Hohre *et al.*); (Mansfeld, Hohre *et al.*, 1998); (Stauss-Grabo, Häberlein *et al.*, 2008); (Stauss-Grabo and Atiye, 2009). The aqueous extract of ivy leaf has been utilized since the nineteenth century in conventional medicine for the treatment of respiratory illnesses. Today, different medication definitions containing dried concentrate of ivy leaf as syrup, effervescent tablets, drops and suppositories are accessible. As of late, the adequacy of this concentrate was likewise tested (Guo, Pittler *et al.*, 2006) (Hofmann, Hecker *et al.*, 2003). Other than catarrh of the upper respiratory tract, the Commission E monograph "Ivy leaves", the ESCOP and the HMPC monograph thus additionally name the symptomatic treatment chronic inflammatory lung disease with symptom of cough as therapeutic indications (Stauss-Grabo, Atiye *et al.*, 2011); (Stauss-Grabo, Atiye *et al.*, 2011); (Stauss-Grabo, Atiye *et al.*, 2011). In 2004,  $\alpha$ -hederin, a remedially involved triterpene saponin Ivy leaf, was distinguished as a key atom for helpful impact (Hegener, Prenner *et al.*, 2004).

This was affirmed by later *in vitro* studies about demonstrating that the mucolytic and steady impacts of ivy on the  $\beta_2$ -adrenergic receptors impacts and this is because of the alpha-hederin and hederacoside C saponins, of which the last alpha-Hederine is used in the body (Sieben, Prenner *et al.*, 2009). Under stimulatory conditions, it hinders intracellular uptake of hederin  $\alpha$  by 2 beta receptors and prompts an expansion in the  $\beta$ -2-adrenergic reaction of the cell. The portrayal of  $\alpha$ -hederin active fixing as an essential atomic level that offers out of the blue a conceivable clarification in the *in vitro* model of the pneumonic impacts of dried concentrate of ivy leaves, which have been seen in various clinical examinations and utilized restoratively in human beings.

Concentrates got from leaves of *Hedera helix* L., are frequently utilized as a part of the treatment of ailments of the upper respiratory tract caused by hyper-emission of thick bodily fluid (i.e., catarrh), and cough. These concentrates were additionally connected as adjuvants for the treatment of inflammatory bronchial disease. Clinical improvements in lung work were established on spirometric and plethysmographic estimations and in addition on related manifestations of cough and sputum were detected (Meyer *et al.*, 1993; (Gulyas, Repges *et al.*, 1997); (Mansfeld, Höhre *et al.*); (Mansfeld, Hohre *et al.*, 1998). In addition, ivy leaves extract is spasmolytic, it reduces smooth muscle spasm, also act as a bronchodilator and antibacterial especially in its saponin triterpene content (Cioaca, Margineanu *et al.*, 1978); (Bedir, Kırmızıpekmez *et al.*, 2000). Saponins are considered substances and were used for the standardization of medicinal herbs (Trute, Gross *et al.*, 1997) *Hedera helix* folium (Stauss-Grabo, Atiye *et al.*, 2011). In this clinical study, we evaluated the combined effects of *H. helix*, *Althea officinalis* and *irio Sisymbrium* on the symptoms of cough, cold and flu. Also, we assessed the safety and efficacy of these herbs.

#### **Ethical approval**

This study was approved by the Departmental Ethical Committee of Medical and Health Sciences Faculty, University of Poonch, Rawalakot, Azad Kashmir.

## **MATERIALS AND METHODS**

#### **Study design**

This was a randomized, single-blind and placebo-controlled clinical study conducted at the Eastern Medicine Clinic University of Poonch, Rawalakot and RHC Paniola Azad Jammu and Kashmir. Patients were unaware of the treatment given to them.

#### **Sample size**

The sample size we selected included 150 patients in total (75 patients in each arm).

#### **Randomization**

Each patient was randomized to a group. Each group contains 75 patients. Randomization was achieved by the consecutive opening impervious closed envelopes with random group assignments.

#### **Inclusion criteria**

- Patients with an acute and chronic cough, cold and flu
- Patients with a dry and productive cough
- Both genders
- Children and adults
- Parent/legally acceptable representative and subject agreed the subject will not use any other cough or cold treatments during the study.
- Having given written informed consent
- Subjects who can understand and are willing to comply to trial instructions
- Satisfactory health except for a cough, cold and flu as determined by the investigator based on medical history and physical examination

#### **Exclusion criteria**

- Patients on a ventilator or have had a tracheostomy and/or endotracheal intubation.
- Blood stained cough/sputum.
- Patients who're not giving informed consent
- Asthmatics presenting with wheeze.
- Current or recent history of the clinically significant medical condition, laboratory abnormality or illness that could place the patient at danger or conciliation the value of the study data as determined by the investigator
- Use of prednisone, narcotic antitussives, inhaled corticosteroids within 2 weeks of Screening
- History of hypersensitivity to any excipient of the applied drugs
- History of chronic gastritis or peptic ulcers
- Diabetes or hypoglycemic disorders.
- A patient who is pregnant or breastfeeding.
- Patients recognized as necessitating conditional or rapid referral.

#### **Study procedure**

During the first visit to randomization, a detailed medical history was obtained with special emphasis on the history of cough, cold, and flu symptoms in all patients. The severity of symptoms of cough, cold, and flu will be assessed through a questionnaire. All patients were randomly assigned to Cough (EMA) granule groups (n = 75) or placebo (n = 75). Each patient received Cough granules (EMA) or placebo sachet thrice daily after meals for one week. The outcome of each group was measured by cough, cold and flu symptoms were associated before treatment and after treatment.

#### **Adverse events**

All adverse events were individualized or determined by patients were documented with information on severity,

**Table 1:** Composition of Cough (EMA) granules

| Ingredient                      | Quantity per 10ml | Common Name   |
|---------------------------------|-------------------|---------------|
| <i>Althea officinalis</i>       | 1000 mg           | Marshmallow   |
| <i>Sisymbrium irio</i>          | 100 mg            | Hedge mustard |
| <i>H.helix</i> powdered extract | 70 mg             | IVY leaf      |

**Table 2:** Comparison of sneezing after treatment in cough (EMA) granules and placebo groups

| Level of Improvement | Complete improved | Moderate improved | Mild improved | No improved | P value |
|----------------------|-------------------|-------------------|---------------|-------------|---------|
| Cough (EMA) granules | 46(61%)           | 15(20%)           | 9(12%)        | 5(7%)       | .0001   |
| Placebo              | 5(7%)             | 13(17%)           | 22(29%)       | 35(47%)     |         |

**Table 3:** Comparison of stuffy nose after treatment in cough (EMA) granules and placebo groups

| Level of Improvement | Complete improved | Moderate improved | Mild improved | No improved | P value |
|----------------------|-------------------|-------------------|---------------|-------------|---------|
| Cough (EMA) granules | 32(43%)           | 22(29%)           | 15(20%)       | 6(8%)       | .0001   |
| Placebo              | 12(16%)           | 14(19%)           | 23(31%)       | 26(35%)     |         |

**Table 4:** Comparison of sore throat/ chest discomfort after treatment in cough (EMA) granules and placebo groups

| Level of Improvement | Complete improved | Moderate improved | Mild improved | No improved | P value |
|----------------------|-------------------|-------------------|---------------|-------------|---------|
| Cough (EMA) granules | 44(59%)           | 19(25%)           | 8(11%)        | 4(5%)       | .0001   |
| Placebo              | 4(5%)             | 17(23%)           | 28(37%)       | 26(35%)     |         |

**Table 5:** Comparison of fatigue/ weakness after treatment in cough (EMA) granules and placebo groups

| Level of Improvement | Complete improved | Moderate improved | Mild improved | No improved | P value |
|----------------------|-------------------|-------------------|---------------|-------------|---------|
| Cough (EMA) granules | 37(49%)           | 23(31%)           | 11(15%)       | 4(5%)       | .0001   |
| Placebo              | 5(7%)             | 17(23%)           | 22(29%)       | 31(41%)     |         |

**Table 6:** Comparison of post nasal drip after treatment in cough (EMA) granules and placebo groups

| Level of Improvement | Complete improved | Moderate improved | Mild improved | No improved | P value |
|----------------------|-------------------|-------------------|---------------|-------------|---------|
| Cough (EMA) granules | 42(56%)           | 24(32%)           | 7(9%)         | 2(3%)       | .0001   |
| Placebo              | 13(17%)           | 15(20%)           | 21(28%)       | 26(35%)     |         |

**Table 7:** Comparison of ache/ pain after treatment in cough (EMA) granules and placebo groups

| Level of Improvement | Complete improved | Moderate improved | Mild improved | No improved | P value |
|----------------------|-------------------|-------------------|---------------|-------------|---------|
| Cough (EMA) granules | 29(39%)           | 20(27%)           | 14(19%)       | 12(16%)     | .0001   |
| Placebo              | 9(12%)            | 5(7%)             | 37(49%)       | 24(32%)     |         |

onset, duration and measures in relation to the study physician. It was accepted that the patient likes to withdraw from the study, regardless of the reason. For patients who withdrew from the study, fights were conducted to determine desertion intent. Lack of compliance (defined as no intake of less than 80.1% of the drugs) has not been established as a treatment failure and the reason for non-compliance.

## STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS version 22 program. The analysis included all subjects randomized in the groups to which they were assigned. The change of the various parameters for the statistical analysis was evaluated through the group analysis at the

entrance and at the end of the study. The paired t-test was used to assess the level of significance. The minimum significance was set at 95% confidence and the p-value <0.05 was considered significant.

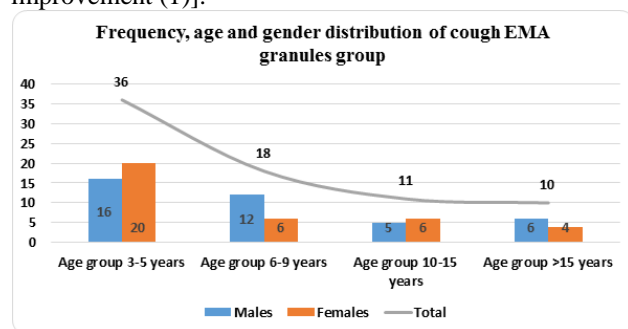
## RESULTS

A total of 150 male and female outpatients (N = 75 Cough (EMA) granules group; N = 75 placebo group) were included in the study. None of the patients stated any adverse or side effect of the study drug. Cough, cold, and flu is considered by positive clinical sign and symptoms of sneezing, stuffy nose, sore throat/chest discomfort, fatigue/weakness, post nasal drip, and ache/pains. Cough, cold and flu is an utmost common respiratory illness in children. Patient's age distribution; sex distribution and

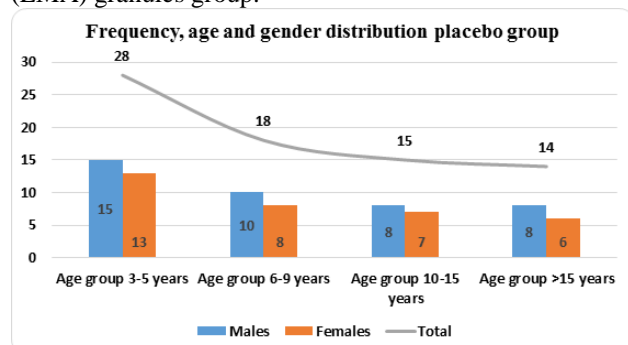
frequency distribution of Cough (EMA) granules group and Placebo group are shown in fig. 1 and fig. 2, respectively.

**Clinical response**

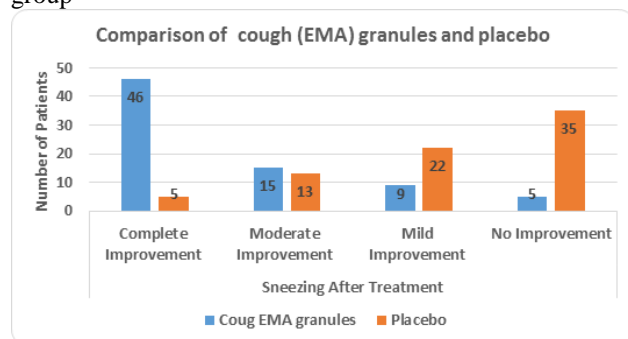
The therapeutic evaluation of the drug was made on the basis of improvement in the subjective signs and symptoms i.e. [Complete improvement (4), moderate improvement (3), mild improvement (2) and no improvement (1)].



**Fig. 1:** Frequency, age, and gender distribution of cough (EMA) granules group.



**Fig. 2:** Frequency, age, and gender distribution placebo group



**Fig. 3:** Comparison of sneezing after treatment in cough (EMA) granules and placebo groups

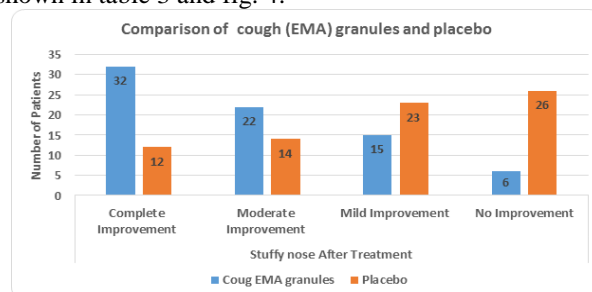
**Sneezing**

Sneezing symptom has been recorded in patients. Patients presenting with the symptom of sneezing observed after treatment in both groups. In Cough (EMA) granules group 61% patients show complete improvement, 20% shows moderate improvement, 12% shows mild improvement and 7% shows no improvement. In Placebo group 7% patient shows complete improvement, 17%

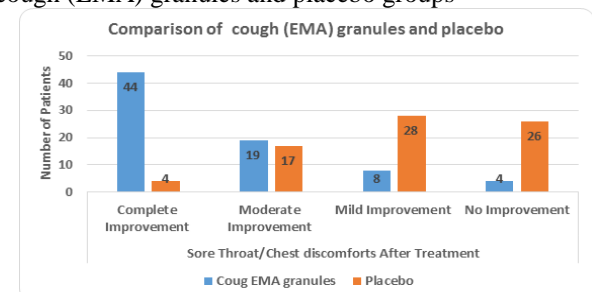
shows moderate improvement, 29% shows mild improvement and 47% shows no improvement. The overall effects of Cough (EMA) granules and Placebo on sneezing after treatment are shown in table 2 and fig. 3.

**Stuffy nose**

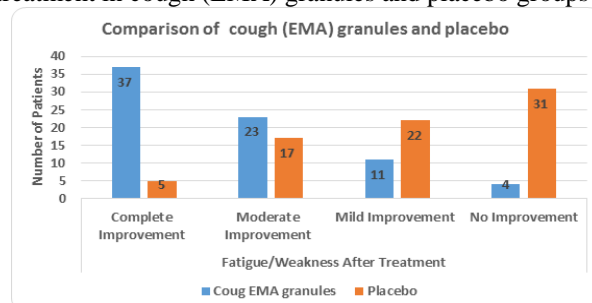
Stuffy nose symptom has been recorded in patients. Patients presenting with the symptom of stuffy nose observed after treatment in both groups. In Cough (EMA) granules group 43% patients show complete improvement, 29% shows moderate improvement, 20% shows mild improvement and 8% shows no improvement. In Placebo group 16% patients show complete improvement, 19% shows moderate improvement, 31% shows mild improvement and 35% shows no improvement. The overall effects of Cough (EMA) granules and Placebo on the stuffy nose after treatment is shown in table 3 and fig. 4.



**Fig. 4:** Comparison of the stuffy nose after treatment in cough (EMA) granules and placebo groups



**Fig. 5:** Comparison of sore throat/ chest discomfort after treatment in cough (EMA) granules and placebo groups

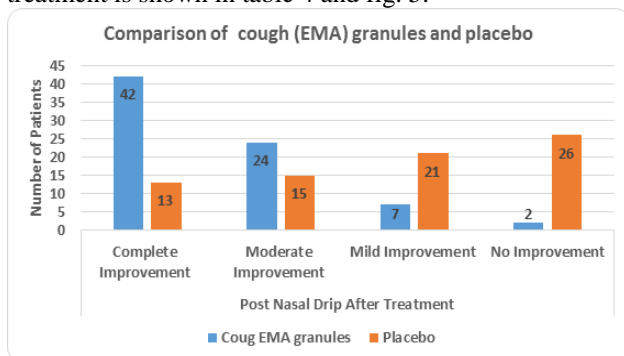


**Fig. 6:** Comparison of fatigue/ weakness after treatment in cough (EMA) granules and placebo groups.

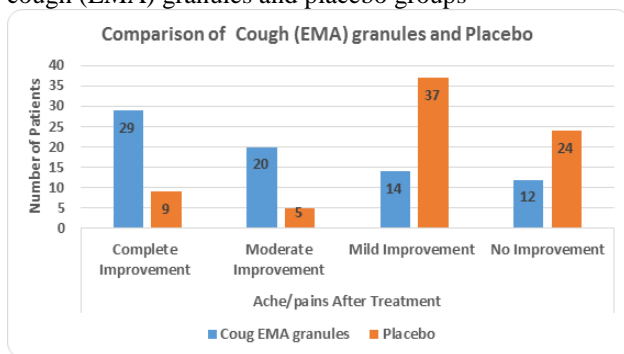
**Sore throat/ Chest discomfort**

Sore throat/ Chest discomfort symptom has been recorded in patients. Patients presenting with symptom of sore throat/ Chest discomfort observed after treatment in both

groups. In Cough (EMA) granules group 59% patients show complete improvement, 25% shows moderate improvement, 11% shows mild improvement and 5% shows no improvement. In Placebo group 5% patient shows complete improvement, 23% shows moderate improvement, 37% shows mild improvement and 35% shows no improvement. The overall effects of Cough (EMA) granules and Placebo on sore throat after treatment is shown in table 4 and fig. 5.



**Fig. 7:** Comparison of post nasal drip after treatment in cough (EMA) granules and placebo groups



**Fig. 8:** Comparison of ache/pain after treatment in cough (EMA) granules and placebo groups

**Fatigue/ weakness**

Fatigue/ Weakness symptom has been recorded in patients. Patients presenting with the symptom of Fatigue/ Weakness observed after treatment in both groups. In Cough (EMA) granules group 49% patients showed complete improvement, 31% shows moderate improvement, 15% shows mild improvement and 5% shows no improvement. In Placebo group 7% patient shows complete improvement, 23% shows moderate improvement, 29% shows mild improvement and 41% shows no improvement. The overall effects of Cough (EMA) granules and Placebo on fatigue/weakness after treatment is shown in table 5 and fig. 6.

**Post nasal drip**

Post nasal drip symptom has been recorded in patients. Patients presenting with symptom of post nasal drip observed after treatment in both groups. In Cough (EMA) granules group 56% patients shows complete improvement, 32% shows moderate improvement, 9%

shows mild improvement and 3% shows no improvement. In Placebo group 17% patient shows complete improvement, 20% shows moderate improvement, 28% shows mild improvement and 35% shows no improvement. The overall effects of Cough (EMA) granules and Placebo on post nasal drip after treatment are shown in table 6 and fig. 7.

**Ache/ pain**

Ache/ Pain symptom has been recorded in patients. Patients presenting with symptom of Ache/ Pain observed after treatment in both groups. In Cough (EMA) granules group 39% patients shows complete improvement, 27% shows moderate improvement, 19% shows mild improvement and 16% shows no improvement. In Placebo group 12% patient shows complete improvement, 7% shows moderate improvement, 49% shows mild improvement and 32% shows no improvement. The overall effects of Cough (EMA) granules and Placebo on body ache/pain after treatment is shown in table 7 and fig. 8.

**DISCUSSION**

The use of antibiotics for respiratory tract infection is a big problem for the society because bacterial resistance is increasing day by day (Fahey, Stocks *et al.*, 1998). Many clinical trials are done on the efficacy of ivy leaf extracts to treat the symptoms of cough and cold. Chemical constituents extracted from ivy leaf have mucolytic spasmolytic and anti-bacterial effects (Gepdiremen, Mshvildadze *et al.*, 2005, Sieben, Prenner *et al.*, 2009). In our study we showed the effectiveness of the combination of ivy leaf with marshmallow and mustard seeds. In one study ivy leaf compared with the placebo, enhancement of the pulmonary function test is seen in ivy leaf group than placebo group (Gulyas, 2006, Mansfeld, Hohre *et al.*, 1998). Ivy leaf compared with the conventional drug ambroxol, patients with chronic bronchitis showed the similar results in both groups (Ali, Daniyal *et al.*, 2017). Marshmallow form a protective layer on the respiratory track and inhibit the coughing and shielding it from irritants (Mueller-Limmroth and Froehlich, 1980). Marshmallow also have spasmolytic bactericidal and antisecretory activity (Mueller-Limmroth and Froehlich, 1980). Mustard seeds widely used in the folk medicine for the treatment of fever, cough rheumatoid arthritis and inflammation (Al-Jaber, 2011). Our study results are corresponding with the pharmacological actions of the ivy leaf, marshmallow and mustard seeds. Cough EMA granules showed a superior result than placebo. The combination of ivy leaf, marshmallow and mustard seeds proved the efficacy in the treatment of cough and cold. No side effect was reported in our study and tolerability of cough EMA granules are comparable to placebo. The overall efficacy and safety of cough EMA granules are outstanding.

## CONCLUSION

For decades, herbal preparations have been used for the treatment of cough. The mechanism of this polyherbal formulation is to relieve inflammation and hypersecretion of gelatinous mucus. This study clearly demonstrated the efficacy of Cough (EMA) granules in the treatment of cough, cold, and flu in children and adults and can be recommended as an adjuvant management of upper respiratory tract disorders. However large scale clinical studies of cough EMA granules are needed in future.

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