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Research Article

Evaluation of Clinical Efficacy and Safety of *Nigella Sativa* Seed Oil added to Standard Treatment in Uncomplicated Respiratory Infection - A Randomised, Open Labelled, and Parallel Arm Study

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A B S T R A C T

Introduction: Nigella sativa, known for its various pharmacological activities, is under trial for COVID-19.

Objectives: The objectives were to assess the efficacy of Nigella Sativa, a traditional herbal medicine, added to standard treatment in the management of uncomplicated respiratory infection in terms of reduction in severity and worsening of clinical symptoms and to assess its safety through the incidence of adverse events.

Method: The study was an open-labelled, parallel-arm, randomised controlled study in 50 participants with uncomplicated respiratory infections. Patients with symptoms of respiratory infections including fever, sore throat, throat pain, rhinitis, headache, myalgia and cough with or without expectoration for 5 days or less, were enrolled in the study. They were randomly allocated to two groups: Group 1 received standard treatment for 7 days and Group 2 Nigella Sativa oil - 1000mg twice daily with standard treatment for 7 days. The patients were physically followed up on day 4 and day 7 after starting treatment. General and systemic examination, assessment of vitals including body temperature, assessment of adverse events and clinical response to treatment were carried out during each visit.

Results: The two groups showed similar efficacy for improvement in clinical symptoms on day 7. But on day 4, more subjects became symptom-free in Group 2 (N. sativa + standard treatment) as compared to Group 1 (standard treatment alone). The incidence of adverse events was similar in both groups and all the adverse events were minor in nature.

Conclusion: Hence it is concluded that the addition of N. sativa to standard treatment could potentially benefit the patients with uncomplicated respiratory infection with early clinical cure.

Keywords: *Nigella Sativa*, Respiratory infection, RCT, Herbal treatment

Introduction

Many traditional medicines, obtained from plants are playing a vital role in the management of respiratory infections caused by bacteria and viruses.[1] There is active research happening globally to find out new drugs, vaccines and repurposing of the existing drugs including the traditional medicines for COVID-19 since the onset of the pandemic. The scientists are exploring the benefits of traditional plants in the management of COVID-19 and other respiratory infections.[2]

Nigella Sativa, also known as black cumin, belonging to the family Ranunculaceae, has been commonly used as a spice in various countries across the globe.It has wide pharmacological actions that include antioxidant, antidiabetic, antihypertensive, neuroprotective, anti-inflammatory, analgesic, antibacterial, antiviral, antifungal and anticancer activities.[3] The phytochemicals present in the seeds of *Nigella Sativa* include thymoquinones, saponins, sterols, alkaloids, novel lipids, fatty acids and volatile oils. The most important biologically active compound among these is thymoquinone.[4]

Thymoquinone, obtained from the *Nigella Sativa* seeds showed an inhibitory effect against various Gram-positive and Gram-negative bacteria such as *Staphylococcus, Streptococcus, Pseudomonas aeruginosa, Klebsiellapneumoniae,Methicillin-resistant Staphylococcus aureus (MRSA), Bacillus, Listeria* and so on.[5-7]

The therapeutic efficacy of *Nigella Sativa* oil in allergic rhinitis has been reported in a few studies. Ansari MA et al., in their randomised controlled study done in patients with allergic rhinitis, found that *N.sativa*seeds when given orally at a dose of 250 mg/ day for 15 days, decreased the clinical symptoms of allergic rhinitis. They also observed a significant reduction in the body temperature in febrile patients.[8] In another study done by IşıkH et al., *N.sativa* seed at a dose of 2 g/ day in patients with allergic rhinitis, showed improvement in clinical symptoms and enhanced the phagocytic activity of polymorphonuclear cells and increased CD8 counts.[9]

At present, a few trials are going on to evaluate the efficacy of *N.sativa* oil in COVID-19, registered in clinicaltrials.gov (Trial registration numbers: NCT04401202, NCT04981743, NCT04767087, NCT04347382, NCT04914767). With this background, the present study was undertaken to evaluate the efficacy and safety of *N.sativa* seed oil, added to standard treatment in uncomplicated respiratory infection.

Objectives

To evaluate the efficacy of *N.sativa* seed oil, added to standard therapy in uncomplicated respiratory infectionusing the following outcome measure:

- Reduction in the severity of clinical symptoms

To assess the safety of *N.sativa* seed oil added to standard treatment using:

- Incidence of adverse events

Materials and Method

The study was approved by Institutional Human Ethics Committee (IHEC approval reference no: IHEC II/0122/21) and conducted as a randomised, open-labelled, parallel-arm study in patients with uncomplicated respiratory infections including common cold, bacterial or viral respiratory infections or flu-like illnesses. The study was carried out in a tertiary care hospital in South India and the study duration was 3 months (from August 2021 to October 2021). Participants attending the outpatient clinics of General Medicine and Respiratory Medicine departments, who fulfilled the following eligibility criteria were included in the study.

Inclusion Criteria

- Age 18 to 65 years, both years inclusive
- Both gender (males and females)
- Subjects with uncomplicated respiratory infections,presenting with symptomsof fever, sore throat, throat pain, rhinitis, headache, myalgia and cough with or without expectoration (for a duration of 5 days or less)
- Subjects with an oxygen saturation of 95% or more
- Willing to give written informed consent
- Subjects with co-morbidities like stable and controlled diabetes mellitus or systemic hypertension or without any significant co-morbidities

Exclusion Criteria

- Subjects with oxygen saturation less than 95%, breathlessness, abnormal auscultatory signs
- Subjects with chronic respiratory problems includingchronic bronchitis, bronchial asthma, and chronic obstructive airway problems
- Subjects with significant cardiovascular,gastrointestinal, neurological, and psychiatric disorders
- Subjects with malignancy involving any organ
- Subjects with known hypersensitivity to the *N.sativa* seed oil and other drugs prescribed
- Pregnant women and breast-feeding mothers
- Subjects positive for COVID-19

50 participants who fulfilled the eligibility criteria were enrolled and they were randomly allocated to two groups (25 in each group). Simple random sampling using computer-generated random number table was applied for randomisation.

After obtaining informed consent, the participants were

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allocated to either of the two groups and received treatment as follows:

Group 1: Standard treatment (antipyretics and/ or levofloxacin and/ or cough remedies and/ or antihistamines and/ or nasal decongestants for3 to 7 days as per the decision of the treating physician)

Group 2: Standard treatment as given in Group 1 +*N.sativa* seed oil capsules (commercially available) 1000 mg, given orally, two times a day.

Study Assessments at Baseline (Day 0)

- Subject demography - age, sex, weight, height and BMI
- Vitals- pulse rate, SpO_2, respiratory rate, body temperature and blood pressure
- Constitutional symptoms - fever, sore throat, throat pain, rhinitis, headache, myalgia and cough
- General examination
- Systemic examination
- CBC (Complete blood count)

After the baseline assessments, treatments were given as detailed above for groups 1 and 2.

The subjects were physically followed up on day 4 and day 7 after starting the treatment. In addition, telephonic follow up was done, every day, from day 1 to 7 to remind the subjects for medication intake and toknow whether the clinical symptoms improved/ worsened and if the subject developed any adverse effect.

During the physical follow-up visits to the hospital on days 4 and 7, the following assessments were done: vitals parameters (pulse rate, SpO_2, respiratory rate, body temperature and blood pressure), general and systemic examination, adverse events, constitutional symptoms and clinical signs. Complete blood count was done at the end of the study on day 7.

The primary objective (reduction in the severity of clinical symptoms) was evaluated with the method used by ArunkumarR et al., in their study that investigated the efficacy of a polyherbal formulation in respiratory infection usinga composite measure of constitutional symptoms, where each of the constitutional symptoms was given a score of 1 if it was present and 0, if not.[10]

In the present study,seven constitutional symptoms such as fever, sore throat, throat pain, rhinitis, headache, myalgia and cough were included for efficacy assessment and hence after adding the score for each symptom, every subject could have a composite score between 0 and 7. The reduction in this composite score from baseline to days 4 and 7 was considered as the primary outcome measure.

Statistical Analysis

Age, height, weight and BMI were compared between the groups using unpaired t-test. Blood parameterswere analysed using paired t-test within the groups and unpaired t-test between the groups. The difference in the proportion of males and females between two groups was compared using chi-square test.

The difference in the vital parameters (pulse rate, SpO_2, respiratory rate, body temperature, and blood pressure) was analysed using repeated measures ANOVA within the groups and one-way ANOVA between the groups.

The difference in the composite score of constitutional symptoms between the groups was compared using one-way ANOVA and within groups using Friedman test.

Results

All the 50 subjects who were enrolled, completed the study and there were no dropouts. The CONSORT (Consolidated Standards for Reporting Trials) participant flow chart is shown in Figure 1.

Gender

The number of males and females did not significantly differ between groups 1 and 2. There were 13 malesand12 females in Group 1 and 15 males and 10 females in Group 2 (p=0.3).

Demographic Characteristics

No statistically significant differences were observed in age, height, weight, and BMI between the groups.

Vitals

The vital parameters were within the normal limits and no clinically significant or statistically significant differences were noted at baseline, on days 4 and 7.The details are given in Table 1.

Body Temperature

The mean body temperature at baseline (day 0), day 4 and day 7 in both the groups is shown in Figure 2.

The reduction in body temperature from baseline to days 4 and 7 was highly significant in both groups ($p < 0.01$, repeated measures ANOVA-within group analysis). When both the groups were compared using One-way ANOVA with Tukey-Kramer multiple comparison test, it was observed that the reduction in body temperature on day 4 was significantly high in Group 2 compared to Group 1 ($p<0.01$). On day 7, the body temperature was almost close to the normal body temperaturein all the subjects in both groups. No statistical significance was observed between groups1 and 2 on day 7 for body temperature.

Among the subjects who had fever at the baseline, there was a significant reduction in the proportion of subjects having fever from baseline to days 4 and 7 in both the groups ($p<0.0001$, Chi-square test - within group analysis).

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As given in Figure 3, on the 4th day, 5 subjects in Group 1 and nosubject (0) in Group 2 had fever while the remaining subjects became afebrile. All the subjects in both groups were afebrile on day 7. No significant difference was observed in terms of number of subjects having fever between the groups at day 0 and day 7($p>0.05$, Chi-square test). But on day 4, there were significantly fewer subjects who were afebrile in Group 2 compared to Group 1 ($p=0.04$, Chi-square test, shown in Table 2).

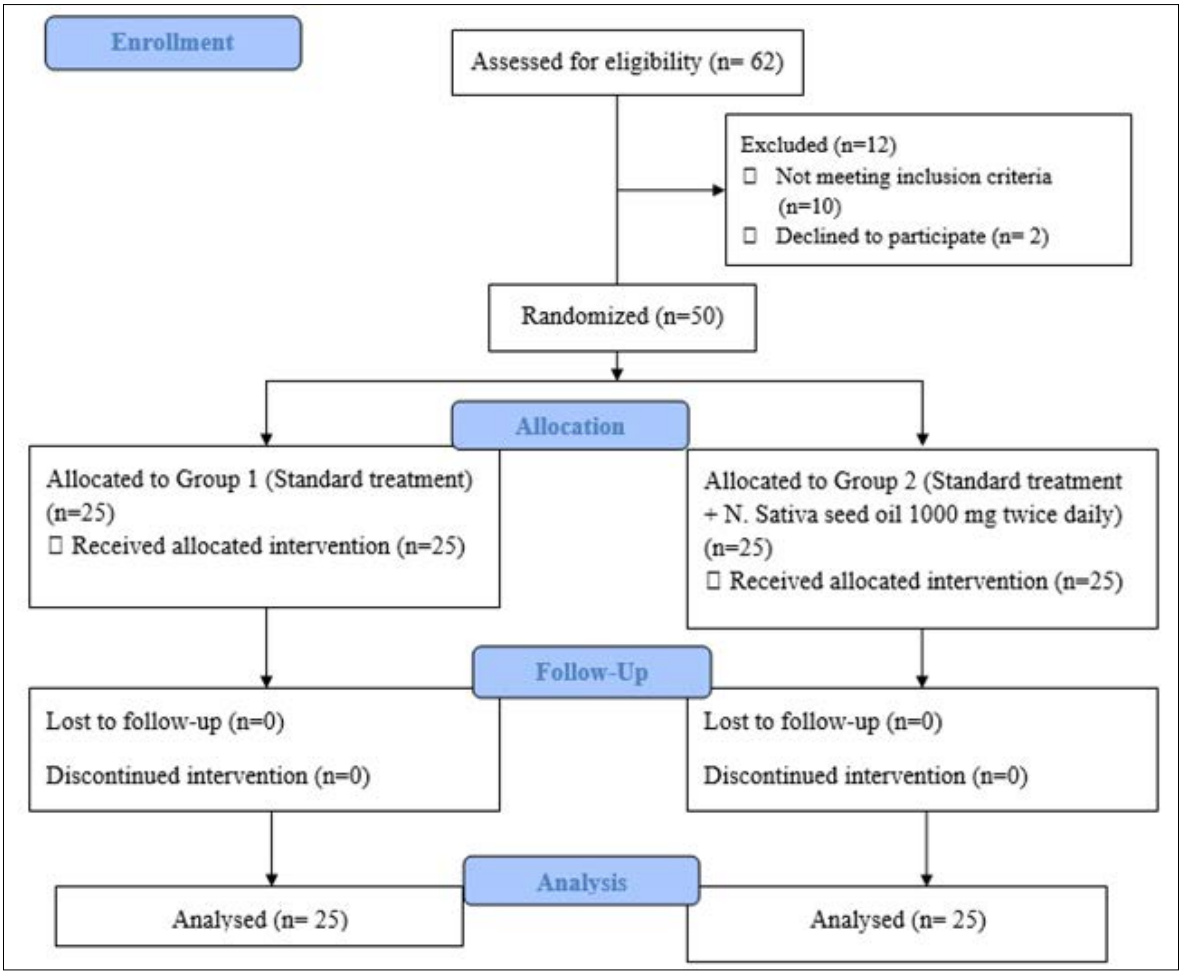

Figure 1.Participant Flow Diagram

Table 1.Vitals

		Group 1			p-value	Group 2			p-value
Days		0	4	7		0	4	7	
Blood pressure (mm Hg)	Systolic (mean SD)	118 (9.43)	119.05 (7.37)	118.56 (14.37)	0.90	116.11 (12.34)	117.11 (9.13)	117.47 (7.39)	0.88
	Diastolic (mean SD)	76.42 (6.86)	74.21 (6.23)	75.68 (6.91)	0.49	72.68 (13.67)	73.53 (7.90)	73.97 (9.52)	0.9
Pulse rate (mean SD)		89.53 (15.64)	86.56 (7.75)	88.12 (10.32)	0.67	84.42 (11.29)	86.53 (8.47)	80.68 (9.78)	0.11
SPO_2		97.97 (2.79)	98.32 (1.65)	98.54 (1.32)	0.61	97.62 (3.73)	98.06 (3.18)	98.04 (3.39)	0.87
Respiratory rate		18.42 (2.39)	18.99 (1.64)	18.63 (1.37)	0.54	18.39 (2.78)	18.48 (1.91)	18.09 (1.55)	0.79

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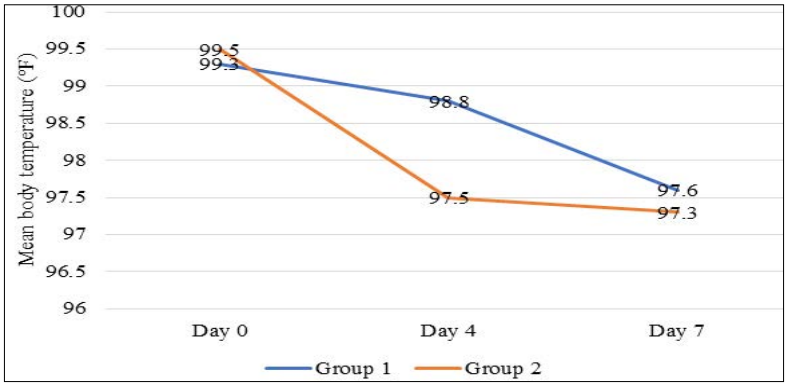

Figure 2.Body Temperature of the Participants

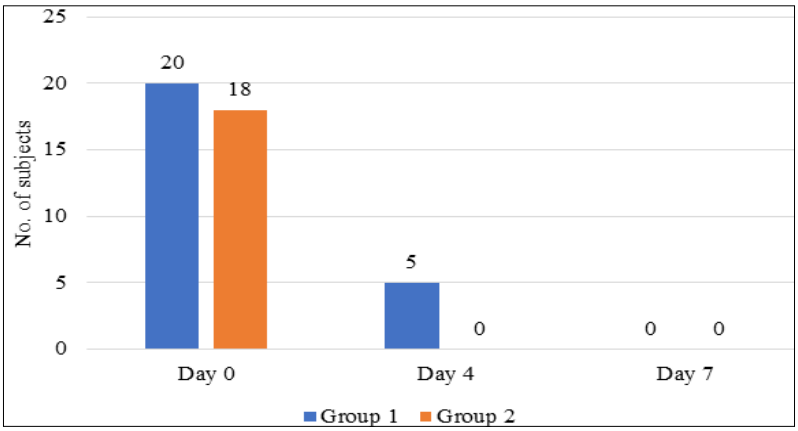

Figure 3.Number of Subjects with Fever

Table 2.Number of Subjects with Constitutional Symptoms

Groups		Group 1				Group 2					
Days		0	4	7	p-value (Group 1) Chi-square test	0	4	7	p-value (Group 2) Chi-square test	p-value (Group 1 vs 2) Day 4 Chi-square test	p-value (Group 1 vs 2) Day 7 Chi-square test
Fever	Yes	20	5	0	<0.0001	18	0	0	<0.0001*	0.04*	>0.05
	No	5	16	25		7	24	25			
Headache	Yes	10	3	0	0.0002	8	0	0	0.0001*	0.2	>0.05
	No	15	22	25		17	25	25			
Rhinitis	Yes	14	7	1	<0.0001	15	1	0	<0.0001*	0.01*	>0.05
	No	11	18	24		10	24	25			
Sore throat	Yes	16	6	0	<0.0001	14	0	0	<0.0001*	0.01*	>0.05
	No	9	19	25		11	25	25			
Throat pain	Yes	15	5	0	<0.0001	13	0	0	<0.0001*	0.04*	>0.05
	No	10	20	25		12	25	25			
Cough	Yes	9	5	1	0.01	8	0	0	0.002*	0.02*	>0.05
	No	16	22	24		17	25	25			
Myalgia	Yes	13	6	0	<0.0001	14	1	0	<0.0001	0.03*	>0.05
	No	12	19	25		11	24	25			
*S|tatisticallysignificant											

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Constitutional Symptoms

The constitutional symptoms included in the study werefever, sore throat, throat pain, rhinitis, headache, myalgia and cough and the respective data is given in Table 2. There was a significant reduction in the number of subjects having the constitutional symptoms from baseline to day 4 and day 7 in both groups. In Group 1, on day 7, 1 subject still had rhinitis and 1 had coughand subsequently, they became asymptomatic with appropriate medical management. None of the subjects in Group 2 had constitutional symptoms on day 7. There was no significant difference noted between the groups with regard to the proportion of subjects having constitutional symptoms on day 7, whereas on day 4, the proportion of subjects with constitutional symptoms was significantly less in Group 2 compared to Group 1 for all the symptoms except headache.

Composite Measure of Constitutional Symptoms

The mean composite score for constitutional symptoms in both groups is shown in Figure 4. A significant reduction in the composite score was observed in both groups (Group 1: p value=0.00002, Group 2: pvalue=0.00006, Friedman's test), which indicates that both the treatments were effective. The reduction in composite score was similar in both the groups as 'between group analysis' did not show any statistically significant difference.

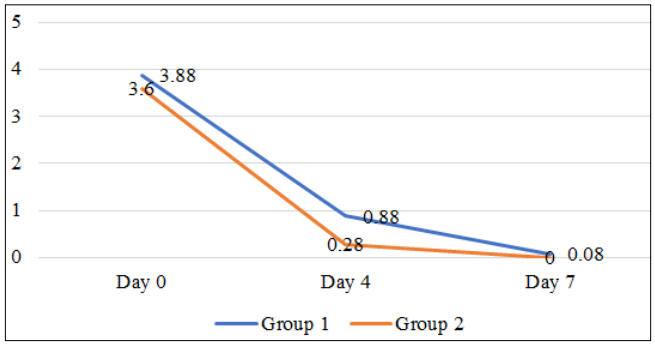

Figure 4.Mean Composite Score of Constitutional Symptoms

Complete Blood Count (CBC)

There was no significant difference observed in the CBC analysis both 'within the groups' before and after treatment (paired t test) and 'between the groups'(unpaired t test). The mean values of all the CBC parameters were within normal limits.

Adverse Events

Overall 3 subjects had adverse events in this study. 2 subjects in Group 1 had loose stools and 1 subject in Group 2 had nausea. The treatments were not stopped due to AEs and they spontaneously resolved in both groups. No serious adverse events were seen in both groups. The proportion of subjects with adverse events between the groups did not differ significantly (p=1.00, Chi-square test).

Discussion

In this study, we evaluated the efficacy and safety of *Nigella Sativa* seed oil when it is added to the standard treatment in uncomplicated respiratory infections. Though both groups showed similar efficacy in reducing the constitutional symptoms,the add-on therapy has resulted in significantly more proportion of subjects showing early symptomatic relief. At the end of treatment, all the subjects in *N.sativa* group were free from the constitutional symptoms whereas 2 subjects in the standard treatment group showed symptoms (1 had rhinitis and the other had cough).

Both the groups showed a significant reduction in the body temperature on days 4 and 7 compared to baseline, but the reduction was highly significant in Group 2 compared to Group 1 on day 4 ($p<0.01$). In Group 1, 25% of subjects remained febrile on day 4 i.e., 5out of 20 subjects who had fever at baseline remained febrile on day 4, whereas none of the subjects had fever on day 4, in Group 2. On day 7, all the subjects in both the groups were afebrile. The trend was similar for other constitutional symptoms as well except for head ache (Table 2), where the proportion of subjects who continued to have other constitutional symptoms on day 4 was comparatively low in Group 2.

The statistical analysis to evaluate the efficacy did not show any significant difference between the groups before and after treatment. But, on day 4, the reduction in the mean body temperature was highly favourable in Group 2 and similarly, the proportion of subjects who became symptom-free was significantly more in Group 2. This shows that the addition of *N.sativa* to standard treatment would result in an early clinical cure compared to standard treatment alone.

There were no serious adverse events observed in both the groups. 2 subjects in the standard treatment group had loose stools and 1 subject in *N.sativa* group had nausea. All the adverse events were mild in nature and resolved spontaneously. The treatment was not stopped due to adverse events. Further, the proportion of subjects having adverse events did not statistically differ between the groups. The safety of *N. sativa* has been established in many clinical studies and in this study also it was well tolerated. Complete blood count assessments did not show any clinically significant differences in both groups.

The above findings are indicative of the potential benefit of adding *N. sativa* to the standard drug treatment for managing uncomplicated respiratory infections as it results in early clinical cure with no significant adverse events. The limitation of this study is that the efficacy was assessed only with the clinical signs and symptoms. Inclusion of other parameters like bacteriological culture with throat

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and nasal swabs, chest x-ray and other outcome measures would give more insightinto the efficacy of *N. sativa*. We have future plans to further investigate these aspects.

Similar to our study, Ansari MA et al., evaluated the efficacy of *N. sativa* seed oil (250 mg/day)in patients with allergic rhinitis and found that the clinical symptoms improved and there was a significant reduction in the body temperature after 15 days of treatment.[8] IsikH et al., evaluated the efficacy of *N. sativa*seed oil at a dose of 2 g/day (same dose used in our study) and found that *N. sativa*improved clinical symptoms and enhanced the phagocytic activity of polymorphonuclear cells and increased the count of CD8 cells.[9]

The trials to assess the efficacy of *N. sativa* in COVID-19 are going on and the results are yet to be published. Once the results of those trials are out and if the efficacy is established, *N. sativa* could emergeas a good treatment option for asymptomatic and mild COVID-19.

Strengths and Limitations

To our knowledge, this is the first study done to evaluate the efficacy of *N. sativa* seed oil in uncomplicated upper respiratory infection with the composite measure of constitutional symptoms as the outcome measure, which would reflect the overall improvement in a patient. Further, the dose of *N. sativa* seed oil used in the study (2 g/day) is the standard dose proven to be effective in the studies that evaluated other properties of *N. sativa*i.e., antioxidant, anti-hypertensive, anti-inflammatory, anti-bacterial and so on.[3]

The limitation of the study is the samplesize. As the study was done only in 50 patients, the inclusion of a larger number of subjects would have added more value to the study. Another limitation is that the intake of study medications was not supervised. The participants were dispensed with the medicines and advised to consume them daily at home. Hence, the drug compliance was assessed as reported by the subjects.

Conclusion

From the results of this study, it can be concluded that the addition of *N. sativa*at a dose of 1000 mg, two times a day, to standard treatment could potentially benefit the patients with uncomplicated respiratory infectionsas it leads toan early clinical cure. Further studies with more subjectsand microbiological and radiological outcomes are needed to reaffirm the efficacy of *N. sativa*.

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Conflict of Interest: None

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