Clinical evaluation of effectiveness of TR-01 in providing relief in productive, non-productive, and bronchial cough

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ABSTRACT

Background: MN Pharmaceutical design and developed the TR-01 syrup for the management of cough and maintain well-being. **Aim:** The aim of the study was to evaluate the clinical effectiveness of TR-01, providing relief from bronchial cough with throat irritation. **Materials and Methods:** A parallel arm, prospective, and randomized clinical study was conducted. Subjects were advised to take a dose of 10 ml of TR-01 thrice daily orally before meal for 4—8 days or until complete resolution of symptoms. The study was to assess the efficacy of herbal syrup with respect to symptomatic relief in the patient suffering from cough, change in the wet and dry cough severity, and pain frequency scores of the subjects were measured. Changes in throat irritation, throat mucosa redness, fever, and Leicester Cough Score were measured. **Results:** Forty-five subjects completed the study. TR-01 was effective in reducing cough severity of cough (within 4 days of administration) of various types such as wet, dry, and bronchial cough that suggests a wide indication for the product, and its useful in the management of various productive, non-productive bronchial cough episodes. There was a significant reduction in cough associated symptoms such as sore throat, mucosal redness, and mucosal itching in single day from the administration of TR-01, suggesting immediate action of the product. Chest discomfort and fever were also predominantly reduced in 4 days of treatment. TR-01 did not produce drowsiness as that of conventional medication for the treatment of cough. **Conclusion:** Thus, "TR-01" produced significant activity in reducing cough and related symptoms in wet, dry, and bronchial cough.

Keywords: Bronchial cough, Leicester Cough Score, parallel arm, randomized, TR-01

Introduction

Cough is considered an important reflex which enhances the clearance of secretions and particles from the airway passages. It protects the airways from the aspiration of foreign materials. It is also considered one of the most common symptoms for which people seek medical attention from their pharmacists, general practitioners, and pulmonologists.[1]

The prevalence of cough in India is 5%–10%. It is one of the most common presenting complaints (30%) at the primary care setting. Cough may adversely affect the quality of life, sleep, and productivity at work. Cough may also lead to urinary incontinence and discomfort.[2]

The use of herbal medicines in cough treatment has gained popularity throughout the world in recent times. Often seen as natural alternatives with fewer side effects than synthetic medicines, these medicinal plants and their phytochemical constituents are thought to have potential applications in the management of a wide range of health conditions.[3]

There should be proper guidelines and clinical studies showing the beneficial effects of herbal medicines in cough management as often

these are self-medication type, including the potential for overdose when there are no clearly established guidelines on dosage, the risk of toxicity.[4]

Classification of cough

Cough is classified according to the length of time that the cough persists. It is classified into acute, sub-acute, and chronic cough; sometimes, it divided in to wet and dry cough as well. It is a real possibility that the underlying disease condition may progress in severity and lead to the progression of acute/sub-acute cough to chronic cough.[5]

Product Description

Key ingredients are described in Table 1.

Study Design

It was a parallel arm, prospective, and randomized clinical study.

Ethics

The clinical trial has been registered on the Clinical Trial Registry of India (CTRI) website having CTRI Number – CTRI/2019/09/021203, registered on September 12, 2019.

Study Objectives

The primary objective of the study was to assess the efficacy of herbal syrup with respect to symptomatic relief in patient suffering from cough, change in the wet cough severity and frequency score, change in the dry cough severity and frequency score and 15 min after the start of treatment on day 1 (telephonic review), day 4, and day 8 or up to complete recovery (whichever is earlier) compared to the baseline. The secondary objective of the study was to assess the change in the chest discomfort score, change in score of throat pain, change in throat irritation/itching, throat mucosal redness, fever, measure of drowsiness, physician's global assessment of efficacy, subject's global assessment of efficacy, and chest X-ray analysis from baseline to end of treatment (only with history of bronchial cough).

Subject inclusion criteria

Male and females subjects between 18 and 65 years of age and diagnosed having cough-dry cough (<14 days) of any origin, acute moderate to severe wet (productive) cough production at a maximum of 14 days before screening of any origin and chronic bronchitis (chronic cough and sputum production on most days for one consecutive months for more than 2 consecutive years) were included in the study. Subjects having presenting symptoms of throat pain, throat redness, throat irritation/itching, and not under any antibacterial or antiviral treatment before recruitment were selected for the study. Subjects ready to abstain from using any drug (which will affect the study outcome) other than the investigational and administration of any herbal or Ayurvedic treatment or gargles directed to ease coughing or throat parameters, tea, and coffee were included in the study. Subjects willing and able to provide a signed written informed consent before any study-specific procedure and subjects who, in opinion of the investigator, will be able to comply with the study requirements were selected for the study.

Subject exclusion criteria

Subjects with H/O underlying lung pathology such as lung abscess and cystic fibrosis; having known hypersensitivity to ingredients of investigational products and H/O myocardial infarction within 4 weeks before enrollment and history of hepatic impairment were not included in the study. Subjects with immediate life-threatening diseases such as pre-existing cardiovascular, liver, or neoplastic disease and having uncontrolled hypertension and known human immunodeficiency virus, Hepatitis B virus, Hepatitis C virus, or tuberculosis infections were excluded from the study. Subjects having history of alcohol, smoke, and drug abuse as well as subjects with occasional consumption were excluded from the study. Subjects on any other herbal therapy/supplement for cough and known to have pregnancy, lactation, and female patients not using acceptable contraceptive measures were not included in the study.

Dosage and treatment duration

10 ml of TR-01 was given thrice daily orally before meal for 4–8 days or until complete resolution of symptoms whichever was earlier. Subjects were advised lifestyle modifications (nutritious diet, exercise, etc.).

Study visits/follow-ups

Screening visit (day 0), visit 1 (day 1), visit 2 (day 4), visit 3 (day 8). Subjects were asked to come for follow-up on the scheduled follow-

Table 1: Description of product

S. No.	Name of ingredients	Botanical name	Plant part	Indication
1.	Adulsa	*Adhatoda vasica*	Leaf	Bronchodilators
2.	Panch tulsi extract	*Ocimum sanctum*	Leaf	Antitussive
3.	Lavang	*Syzygium aromaticum*	Buds	Anti-inflammatory
4.	Kantkari	Solanum xanthocarpum	Fruits	Bronchodilators
5.	Kulinjan	*Alpinia galanga*	Whole plant	Antihistaminic
6.	Shunthi	*Zingiber officinale*	Zhiromes	Antibacterial
7.	Bharangmool	*Clerodendrum serratum*	Whole plant	Soar throut
8.	Jethimadh	*Glycyrrhiza glabra*	Stems	Antiulcer (soothing)
9.	Pippali	*Piper longum* (Bioavailability enhancer)	Fruits	Bioavailability enhancer
10.	Nagarmotha	*Cyperus rotundus*	Roots	Antipyretic, analgesic,
11.	Dalchini	*Cinnamomum zeylanicum*	Stems	Antibacterial effects
12.	Olive leaf extract	Olive leaf extract	Leaf	Antioxidant

up visit time. A screening window of up to 2 days was kept, in case if there was delay in availability of tests reports or in case few tests needed to be repeated.

Study Procedures

Written informed consent was obtained from the interested subjects before screening for possible inclusion in the study. During the informed consent process, they were given enough time to read informed consent document, which was printed in the languages best understood by them. Subjects were given the freedom to ask the questions, and all questions were answered by the investigator or by other study staff. If he/she agreed to participate in the study, written informed consent for the same was obtained from him/her.

Subjects identified as having cough (dry cough, wet cough, and bronchial cough) were screened for recruitment. On screening visits (up to day-2), written informed consent was obtained from subject for his/her participation in the study. The subject underwent physical and systemic examinations. The subject's medical and surgical history was taken. Subject's current medication, if any was noted in the subject, was called the next day morning on an empty stomach for laboratory investigations.

Subject's investigations complete blood count (CBC) and chest X-ray (bronchial cough patient only) were done. Subject's data regarding conventional treatment were recorded. Furthermore, subjects were advised to refrain from any nutraceutical, Ayurvedic, homeopathic, Siddha, Unani, etc., treatment for cough. A screening window of up to 2 days was kept in case if there was a delay in the availability of test reports or in case few tests needed to be repeated. Subjects were called on the baseline visit (day 0). On baseline visit, subjects were recruited if he/she met all the inclusion criteria. Subjects underwent general and systemic examinations and symptom gradation. Subjects were instructed to consume TR-01 herbal syrup before meal. Subjects were advised to follow visit schedule, i.e., days 1, 4, and 8, respectively, after consumption of TR-01 herbal syrup. Subjects were given medication packed in an Amber color Pet Bottle containing 100 ml of syrup. Subjects were allowed to come for follow-up on the scheduled follow-up visit, provided subject consumed the given treatment. Subjects were called on day 1 for the first follow-up visit.

All the subjects were closely monitored for any adverse events (AE). If the subject had AE/serious adverse event (SAE), the details of the incidence were documented in the source document and case report form (CRF). SAE, if any, was reported to the Institutional Ethics Committee in a SAE reporting form. Rescue medication used, if any, was recorded in the CRF. Subjects were advised not to consume alcohol, caffeine, tea, coffee, and nicotine during the study period. Subjects underwent general and systemic examinations, clinical symptom gradation. On every follow-up visit, change in the wet and dry cough severity and pain frequency scores of the subjects were measured. Changes in throat irritation, throat mucosa redness, and fever were measured. The Leicester Cough questionnaire was filled by the patient on every follow-up visit. The container provided to the subject on the previous visit was collected and remaining syrup

was measured to check missed dosage. Subjects who missed dosing partially or completely were treated as drop outs.

On day 8 visit, blood sample was collected and assessed for CBC and chest X-ray (bronchial cough patient only). Changes in the wet and dry cough severity and pain frequency scores of the subjects were measured. Changes in throat irritation, throat mucosa redness, and fever were measured. The Leicester Cough questionnaire was filled by the patient on the last follow-up visit. On day 8, the subject's global evaluation for overall improvement and investigator's global evaluation for overall improvement were done. The subject's tolerability toward TR-01 herbal syrup was assessed. Subjects were advised not to consume alcohol, caffeine, tea, coffee, and nicotine during the study period.

Statistics

Sample size calculation was derived based on the primary endpoint, i.e., change in the wet and dry cough severity and pain frequency scores; changes in throat irritation, throat mucosa redness, and fever. The software used for calculation of sample size was SPSS version 10.0. Primary efficacy endpoints and secondary endpoints were analyzed using per-protocol analysis. Primary endpoints taken under consideration were changed in the wet and dry cough severity and pain frequency scores; changes in throat irritation and throat mucosa redness. Parameters were compared from baseline to each visit and end of therapy using student paired t-test. Data were analyzed by one-way ANOVA followed by selective multiple comparison test. Secondary efficacy parameters such as percentage change in subjective clinical signs and symptoms from baseline to each visit and end of therapy were analyzed and tested by Chi-square test.

Results

Out of 45 completed subjects, 24 were male subjects with the mean age of 39.53 ± 10.31 years. The age range for subjects was 29–49 years. Twenty-one were female subjects with the mean age of 38.20 ± 10.47 years. The age range for subjects was 28–48 years. When compared between the sex and age between male and female groups, the difference was statistically insignificant. The details are presented in Table 2.

Efficacy Assessments

Change in dry cough severity

At the baseline visit, all 15 subjects with dry cough were presenting severe dry cough severity after 1 day treatment three subjects got

Table 2: Demographic details

Parameters	Males	Females
No. of cases	24	21
At age (years)		
Mean	39.53	38.20
SD	10.31	10.47
Range	29–49 years	28–48 years

moderate symptoms and on day 4 there were eight subjects with moderate dry cough severity and seven with mild dry cough severity. On the last day of treatment (8th day) there were eight subjects showing mild dry cough severity and seven with no dry cough. Values are depicted in Table 3. There was a significant change in number of subjects presenting symptoms of dry cough from severe to no symptom.

Change in dry cough chest discomfort

At the baseline visit, ten subjects with dry cough were presenting severe chest discomfort, four with moderate, and one with no chest discomfort. After 1 day treatment, three subjects got moderate symptoms and on day 4 there were six subjects with no chest discomfort. On the last day of treatment (8th day), there were ten subjects showing no chest discomfort and five with mild chest discomfort. Values are depicted in Table 4. There was significant change in the number of subjects presenting symptoms of chest discomfort from severe to no symptom.

Change in dry cough throat pain

At the baseline visit, 11 subjects with dry cough were presenting moderate throat pain, four with mild throat pain. After 1 day treatment, 14 subjects were experiencing mild symptoms and on day 4 there were four subjects with no throat pain. On the last day of treatment (8th day), there were 12 subjects showing no throat pain and three with mild throat pain. Values are depicted in Table 5. There was significant change in number of subjects presenting symptoms of throat pain from severe to no symptom.

Change in dry cough throat itching

At the baseline visit, nine subjects with dry cough were presenting severe throat itching, five with moderate, and one with mild throat itching. After 1 day treatment, nine subjects were experiencing mild symptoms and on day 4 there were four subjects with no throat

itching. On the last day of treatment (8th day), there were 13 subjects showing no throat itching and two with mild throat itching. Values are depicted in Table 6. There was significant change in number of subjects presenting symptoms of throat itching from severe to no symptom.

Change in dry cough throat mucosal redness

At the baseline visit, 11 subjects with dry cough were presenting moderate throat mucosal redness, four with mild throat mucosal redness. After 1 day treatment, 11 subjects were experiencing mild symptoms and on day 4 there were eight subjects with no throat mucosal redness. On the last day of treatment (8th day), there were 13 subjects showing no throat mucosal redness and two with mild throat mucosal redness. Values are depicted in Table 7. There was significant change in number of subjects presenting symptoms of throat mucosal redness from severe to no symptom.

Change in dry cough fever grading

At the baseline visit, seven subjects with dry cough were presenting severe graded fever, four with mild, and four with moderate gradation. After 1 day treatment, nine subjects were experiencing no fever and 12 with no fever on day 4. On the last day of treatment (8th day), all 15 subjects were presenting normal body temperature and no fever. Values are depicted in Table 8. There was a significant change

Table 5: Change in dry cough throat pain

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	0	0	0	0
2	11	0	1	0
1	4	14	11	3
0	0	1	4	12

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

Table 3: Change in dry cough severity

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	15	12	0	0
2	0	03	8	0
1	0	0	7	8
0	0	0	0	7

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

Table 6: Change in dry cough throat itching

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	9	2	0	0
2	5	9	6	0
1	1	4	5	2
0	0	0	4	13

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

Table 4: Change in dry cough chest discomfort

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	10	9	1	0
2	4	3	5	0
1	0	3	3	5
0	1	0	6	10

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P=0.000261$, i.e.,<0.001

Table 7: Change in dry cough throat mucosal redness

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	0	0	0	0
2	11	0	0	0
1	4	11	7	2
0	0	4	8	13

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

in number of subjects presenting symptoms of fever from severe to no symptom.

Change in dry cough Leicester Cough score

At the baseline visit, mean Leicester Cough score was 23.53 ± 4.09. It increased 53.67 ± 18.45, 69.87 ± 12.68, and 120.80 ± 4.48 from days 1, 4, and 8, respectively.

Change in wet cough severity

At the baseline visit, all 15 subjects with wet cough were presenting severe wet cough severity after 1 day treatment eight subjects got moderate symptoms and on day 4 there were five subjects with moderate wet cough severity and ten with mild wet cough severity. On the last day of treatment (8th day), there were five subjects showing mild wet cough severity and ten with no wet cough. Values are depicted in Table 9. There was significant change in the number of subjects presenting symptoms of wet cough from severe to no symptom.

Change in wet cough chest discomfort

At the baseline visit, ten subjects with wet cough were presenting severe chest discomfort, four with moderate, and one with no chest discomfort. After 1 day treatment, six subjects got moderate symptoms and on day 4 there were six subjects with no chest discomfort. On the last day of treatment (8th day), there were 14 subjects showing no chest discomfort and one with mild chest discomfort. Values are depicted in Table 10. There was a significant change in number of subjects presenting symptoms of chest discomfort from severe to no symptom.

Change in wet cough throat pain

At the baseline visit, ten subjects with wet cough were presenting moderate throat pain, four with moderate throat pain. After 1 day

treatment, four subjects were experiencing mild symptoms and on day 4 there were four subjects with no throat pain. On the last day of treatment (8th day), there were 14 subjects showing mild throat pain and one with no throat pain. Values are depicted in Table 11. There was a significant change in the number of subjects presenting symptoms of throat pain from severe to no symptom.

Change in wet cough throat itching

At the baseline visit, nine subjects with wet cough were presenting severe throat itching, five with moderate, and one with mild throat itching. After 1 day treatment, 11 subjects were experiencing mild symptoms and on day 4 there were three subjects with no throat itching. On the last day of treatment (8th day), there were ten subjects showing no throat itching and five with mild throat itching. Values are depicted in Table 12. There was a significant change in the number of subjects presenting symptoms of throat itching from severe to no symptom.

Change in wet cough throat mucosal redness

At the baseline visit, nine subjects with wet cough were presenting moderate throat mucosal redness, one with mild throat mucosal redness. After 1 day treatment, nine subjects were experiencing mild symptoms and on day 4 there were 11 subjects with mild throat mucosal redness. On the last day of treatment (8th day), there were

Table 8: Change in dry cough fever grading

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	7	0	0	0
2	4	5	1	0
1	4	1	2	0
0	0	9	12	15

Assessment of symptoms (*Grades-0=None (97.5–99°F), 1=Mild (99.5–100.5°F), 2=Moderate (101–101.5°F), and 3=Severe (101.5–102°F), data were analyzed by Chi-square test with $P=0.0019$, i.e., <0.01

Table 9: Change in wet cough severity

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	15	7	0	0
2	0	8	5	0
1	0	0	10	5
0	0	0	0	10

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

Table 10: Change in wet cough chest discomfort

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	10	6	1	0
2	4	6	3	0
1	0	3	5	1
0	1	0	6	14

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by the Chi-square test with $P=0.000261$, i.e., <0.001

Table 11: Change in wet cough throat pain

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	10	0	0	0
2	4	1	6	0
1	1	5	5	14
0	0	9	4	1

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

Table 12: Change in wet cough throat itching

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	9	0	0	0
2	5	11	5	0
1	1	4	7	5
0	0	0	3	10

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with $P<0.00001$

13 subjects showing no throat mucosal redness and two with mild throat mucosal redness. Values are depicted in Table 13. There was significant change in the number of subjects presenting symptoms of throat mucosal redness from severe to no symptom.

Change in wet cough fever grading

At the baseline visit, nine subjects with wet cough were presenting severe graded fever, two with mild, and four with moderate gradation. After 1 day treatment, ten subjects were experiencing no fever and 12 with no fever on day 4. On the last day of treatment (8th day), all 15 subjects were presenting normal body temperature and no fever. Values are depicted in Table 14. There was a significant change in the number of subjects presenting symptoms of fever from severe to no symptom.

Change in wet cough Leicester Cough score

At the baseline visit, mean Leicester Cough score was 24.73 ± 3.81. It increased gradually 38.13 ± 10.90, 85.47 ± 21.31, and 97.0 ± 4.31 from days 1, 4, and day 8, respectively.

Change in bronchial cough severity

At the baseline visit, all 15 subjects with bronchial cough were presenting severe bronchial cough after 1 day treatment five subjects got moderate symptoms and on day 4 there were seven subjects with moderate bronchial cough severity and eight with mild bronchial cough severity. On the last day of treatment (8th day), there were two subjects showing mild bronchial cough severity and 13 with no bronchial cough. Values are depicted in Table 15. There was a significant change in the number of subjects presenting symptoms of bronchial cough from severe to no symptom.

Change in bronchial cough chest discomfort

At the baseline visit, 12 subjects with bronchial cough were presenting severe chest discomfort, two with moderate, and one

with no chest discomfort. After 1 day treatment, five subjects got moderate symptoms and on day 4 there were six subjects with no chest discomfort. On the last day of treatment (8th day), there were five subjects showing no chest discomfort and ten with mild chest discomfort. Values are depicted in Table 16. There was a significant change in the number of subjects presenting symptoms of chest discomfort from severe to no symptom.

Change in bronchial cough Leicester Cough score

At the baseline visit, mean Leicester Cough score was 31.45 ± 3.47. It increased gradually from 49.20 ± 8.69, 94.5 ± 12.41, and 105.5 ± 5.8 from days 1, 4, and 8, respectively.

Assessment of global evaluation for overall improvement by an investigator

In test group, $n = 45$, 36 (80%) subjects reported very much overall improvement and 9 (20%) subjects reported much overall improvement at the end of the study as per investigator assessment [Table 17].

Table 13: Change in wet cough throat mucosal redness

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	5	0	0	0
2	9	5	0	0
1	1	9	11	2
0	0	1	4	13

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with *P*<0.00001

Table 14: Change in wet cough fever grading

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	9	0	0	0
2	4	4	2	0
1	2	1	1	0
0	0	10	12	15

Assessment of symptoms (*Grades-0=None (97.5–99°F), 1=Mild (99.5–100.5°F), 2=Moderate (101–101.5°F), and 3=Severe (101.5–102°F), data were analyzed by Chi-square test with *P* 0.0019, i.e., <0.01

Table 15: Change in bronchial cough severity

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	15	3	0	0
2	0	5	7	0
1	0	7	8	2
0	0	0	0	13

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with *P*<0.00001

Table 16: Change in bronchial cough chest discomfort

Score	No. of subjects			
	Baseline	Day 1	Day 4	Day 8
3	12	8	1	0
2	2	5	3	0
1	1	2	5	10
0	0	0	6	5

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe), data were analyzed by Chi-square test with *P*<0.001

Table 17: Global assessment for overall improvement by the investigator

Assessment	Test group (n=30)	
	No.	%
Not assessed	-	-
Very much improved	36	90
Much improved	09	10
Minimally improved	-	-
No change	-	-
Minimally worse	-	-
Much worse	-	-
Very much worse	-	-

Global assessment for overall improvement by subject

In test group, *n* = 45, 41 (91.11%) subjects reported very much overall improvement and 4 (8.88 %) subjects reported much overall improvement at the end of the study as per subject assessment [Table 18].

Tolerability of study drug by physician

As per physician, in test group, *n* = 45, physician reported excellent tolerability of study drugs for 45 (100%) at the end of the study as per physician assessment. The details are presented in Table 19.

Tolerability of study drug by subjects

As per subjects in the test group, *n* = 45, 36 (80%) subjects reported excellent tolerability of study drugs and 9 (20%) subjects reported tolerability of study drugs at the end of the study as per physician assessment. The details are presented in Table 20.

Profile of AE

The analysis reveals that 20% (09 subjects) had AE such as headache, hyperacidity, and body ache with 16 AE out of nine patients. These AE were not probably related to study drugs. There was no need to discontinue the test drug. These AE were mild to moderate in nature. These AE were resolved completely after rescue medication is given in Table 21.

Discussion

Respiratory diseases being very common in human being it's very important to have the management tools which are less costly, effective, with less side effects; Ayurveda precedes the list with its age-old ingredients.

The cough syrup manufactured by MN Pharmaceuticals (TR-01) is having its formula as legacy and amalgamation of old wisdom and modern-day technology to bring the fullest potential of the product. TR-01 has proved effective in dry, wet, and bronchial cough to reduce cough and associated symptoms. The activity to the product is by virtue of the selection of ingredients, selection of the specification of the extracts and effective manufacturing process.

Raisin used as syrup base in the formulation is an age-old treasure from the Ayurveda. From Ayurvedic perspective, its beneficial in many of the following conditions:

Vitis vinifera Linn, otherwise known as raisins, has been a common ingredient used in many ways in Ayurveda. It is encouraged to mix healing foods, such as raisins, into keep healthy and recover fast from diseases. It helps balance *vata* and *kapha*. It is lubricating to respiratory system. It is considered as a brain food good for mental well-being. It is known to increase energy levels. These are some of the activities of raisin which are useful in the common cough and cold where the immunity is being challenged and the energy imbalance can reduce

Table 18: Global assessment for overall improvement by subject

Assessment	Test group (*n*=30)	
	No.	%
Not assessed	-	-
Very much improved	41	91.11
Much improved	4	8.88
Minimally improved	-	.
No change	-	-
Minimally worse	-	-
Much worse	-	-
Very much worse	-	-

Table 19: Tolerability of study drugs assessed by the physician

Assessment	Test group (*n*=30)	
	No.	%
Excellent	45	100
Good	-	-
Fair	-	-
Poor	-	-

Table 20: Tolerability of study drugs assessed by subjects

Assessment	Test group (*n*=30)	
	No.	%
Excellent	36	80
Good	9	20
Fair	-	-
Poor	-	-

Table 21: Profile of adverse events

Events	Test group	
	No.	%
Headache	5	31.25
Hyperacidity	6	37.5
Body ache	5	31.25
No. of patients	09	20.00
No. of events	16	

the rate of recovery. Raisin rich product like TR-01 can improve on energy levels together with soothing effects on respiratory tract and altogether with its antioxidant and antibacterial effect.[6]

Tulsi (*Ocimum sanctum*) is perhaps one of the best examples of Ayurveda's holistic lifestyle approach to health. Tulsi tastes hot and bitter and is said to penetrate the deep tissues, dry tissue secretions, and normalize kapha and vata. Daily consumption of tulsi is said to prevent disease, promote general health, well-being, and longevity and assists in dealing with the stresses of daily life.[7]

Tulsi has got a profound effect in increasing interleukin-4 and interferon-gamma in an immune challenge. Data revealed from

clinical trial Tulsi extract have immunomodulatory effects in healthy volunteers without any side effects.[8]

Panch tulsi is a blend of five species of ocimum and possesses pharmacological activities as useful in all types of allergies, infections, cough, and cold.

Clove is an important medicinal plant due to the wide range of pharmacological effects consolidated from traditional use for centuries and reported in the literature.

The antimicrobial activities of clove have been proved against several bacterial and fungal strains. Anti-inflammatory and analgesic activity of the clove is its local action and can contribute to reduce cough reflex and throat pain in human subjects.[9]

Solanum xanthocarpum, i.e., Kantakari is widely used to treat respiratory diseases in Ayurveda. In references to previously collected information about the probable action of herb, a pilot study was undertaken to investigate the clinical efficacy and safety of the same in bronchial asthma. The respiratory functions (forced vital capacity, forced expiratory volume at 1, peak expiratory flow rate, and forced expiratory flow 25–75%) were assessed using a spirometer before and 2 h after oral administration of 300 mg powder of whole plant of either *Solanum xanthocarpum* or *Solanum trilobatum*. Standard bronchodilator drugs, salbutamol (4 mg), and deriphyllin (200 mg) were used for comparison. Treatment with *Solanum xanthocarpum* significantly improved the various parameters of pulmonary function in asthmatic subjects. The probable mechanism could be the antihistaminic activity of the plant. The same could be beneficial in reducing cough without rendering drowsiness.[10]

Alpinia galangal (Family: Zingiberaceae), i.e., Kulin janis a well-known medicinal herb used for the remedy of various disorders. Conventionally, rhizome of *A. galangal* is used as anti-tubercular, hypothermia, bronchial catarrh, antimicrobial, expectorant, reduce sputum, dilates bronchioles, and reduce asthma.[11]

Zingiber officinale, i.e., Sunthi possesses strong antibacterial, anti-inflammatory, and antioxidant activity by virtue of which, in TR-01, the product demonstrates warmth in throat, reduction in sore throat, and local antibacterial activity to reduce cough severity.[12]

Glycyrrhiza glabra, i.e., Yashtimadhu is widely used traditional ingredient for respiratory disorders. It possesses antiulcer, soothing effects on inflamed mucosa thus relieves soreness in throat and irritation together it has to go excellent activity as an antioxidant and adaptogenic to reduce stress-induced inflammatory responses associated with asthma, and allergic, cough.[13]

Pipalli by virtue of Piperine as a chemical constituent is an excellent bio enhancer to potentiate absorption and action of other ingredients used together in the management of cough asthma and allergy.

According to the Ayurveda, C. rotundus rhizomes, i.e., nagarmotha, are considered astringent, diaphoretic, diuretic, analgesic, antispasmodic,

aromatic, carminative, antitussive, emmenagogue, litholytic, sedative, stimulant, stomachic, vermifuge, tonic, and antibacterial.

Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils. It is used in TR-01 for its anti-inflammatory, antioxidant potential. It contributes to taste of the product in a big way.[14]

Olive leaf is being explored globally for its epithelial recovering and healing properties in mucosal inflammation. It is proven to be an excellent antioxidant and antihistaminic potential that could contribute to the cough management activity of TR-01.

Conclusion

The study was designed to evaluate the safety and efficacy of TR-01 a polyherbal formulation developed and manufactured by MN Pharmaceuticals. TR-01 was effective in reducing cough severity of cough (within 4 days of administration) of various types such as wet, dry, and bronchial cough that suggests a wide indication for the product and its useful in the management of various productive, non-productive bronchial cough episodes. There was a significant reduction in cough associated symptoms such as sore throat, mucosal redness, and mucosal itching in a single day from the administration of TR-01, suggesting immediate action of the product.

Comprehensively, TR-01 was safe and well-tolerated product. TR-01 produced significant activity in reducing cough and related symptoms in wet, dry, and bronchial cough.

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