ejpmr, 2019,6(12), 508-519

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

CLINICAL STUDY TO EVALUATE THE EFFICACY & SAFETY OF CURCUMIN CAPSULE IN PATIENTS WITH COUGH DUE TO CHRONIC BRONCHITIS

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Article Received on 21/10/2019 **Article Revised on 11/11/2019** **Article Accepted on 01/12/2019**

ABSTRACT

Background: Bronchitis is a term that describes inflammation of the bronchial tubes (bronchi and the smaller branches termed bronchioles) that results in excessive secretions of mucus into the tubes, leading to tissue swelling that can narrow or close off bronchial tubes. Bronchial tubes extend from the trachea and terminate at the alveoli in the lungs. The bronchial system resembles an inverted tree and is sometimes termed the "bronchial tree." A few authors include the trachea and upper airway in the definition of bronchitis. There are two major types of bronchitis, acute and chronic. Chronic bronchitis differs from acute bronchitis in several ways, for example, pathology, progression of disease, major causes, treatments, and prognosis. Recurrent incidences of acute bronchitis are the first steps that can lead to developing chronic bronchitis, according to some doctors and researchers. Chronic bronchitis is defined as a cough that occurs every day with sputum production that lasts for at least 3 months, two years in a row. This definition was developed to help select uniform patient populations for research purposes, for example, to study medication therapies for treatment of chronic bronchitis. **Objectives:** To assess the efficacy and safety of Curcumin capsule in Patients with cough due to Chronic Bronchitis. **Conclusion**: The study concludes that, TEST (CURCUMIN) due to its anti-inflammatory and immunomodulatory effect it is more efficacious and safer in comparison to PLACEBO (B) in treatment of cough due to chronic bronchitis and also alleviating the symptoms of chronic bronchitis along with improvement in immunity.

KEYWORDS: Forced Expiratory Volume-One Second (FEV1).

INTRODUCTION

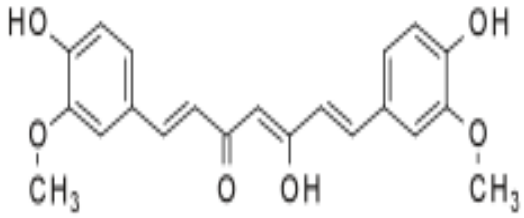
Chronic bronchitis

Chronic bronchitis is defined as a cough that occurs every day with sputum production that lasts for at least 3 months, two years in a row. This definition was developed to help select uniform patient populations for research purposes, for example, to study medication therapies for treatment of chronic bronchitis.

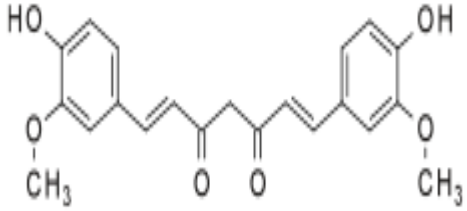
Many of the bronchi develop chronic inflammation with swelling and excess mucus production. The inflammation causes a change in the lining cells of the airways to varying degrees. Many cells that line the airway lose the function of their cilia (hair-like appendages that are capable of beating rapidly), and eventually the ciliated cells are lost. Cilia perform the function of moving particles and fluid (usually mucus) over the lining surface in such structures as the trachea, bronchial tubes, and nasal cavities to keep these hollow structures clear of particles and fluids. These ciliated cells that help in clearance of secretions are often replaced by so-called goblet cells. This group of cells secretes mucus into the airway. The warm moist environment of the airway along with the nutrients in the mucus is an excellent medium for growing bacteria. The mucus often becomes infected and discoloured from the bacterial overgrowth and the body's inflammatory response to it. The inflammation, swelling, and mucus frequently and significantly inhibit the airflow to and from the lung alveoli by narrowing and partially obstructing the bronchi and bronchioles.

Description

Curcumin is a diarylheptanoid. IUPAC name is (1E, 6E)-1, 7-Bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione. Its molecular formula is $C_{21}H_{20}O_6$ and molecular weight is 368.38. It is the principal curcuminoid of turmeric, which is a member of the ginger family (Zingiberaceae). Turmeric's other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The Curcuminoids are natural phenols that are responsible for the yellow colour of turmeric. Curcumin can exist in several tautomeric forms, including a 1, 3-diketo form and two equivalent enol forms. The enol form is more energetically stable in the solid phase and in solution.



Curcumin- Enol Form



Curcumin- keto Form

OBJECTIVES

Primary Objective: To assess the efficacy of Curcumin capsule in Patients with cough due to Chronic Bronchitis.

Secondary Objective: To evaluate the safety of Curcumin capsule in Patients with cough due to Chronic Bronchitis

METHODS

Inclusion Criteria

Male & Female Volunteers, between 18 to 60 years and Diagnosed of chronic bronchitis (chronic cough and sputum production on most days for three consecutive months for more than two consecutive years). Score greater than or equal to 3 points on the cough severity score. Patient having low immunity tested for Immunoglobin antibody (IgG and total IgM & IgE). Patient provided informed consent and willing to comply with all trial requirements.

Exclusion Criteria

Pregnancy or risk of pregnancy, who are on ACE inhibitor drugs, having history of GERD, with asthma, COPD, pneumonia was excluded from the study. Any pathology or past medical condition that can interfere with this protocol, History Presence of the following diseases (like cholangitis, pancreatitis, etc.) or uncontrolled severe organ disorders, Severe neurological or psychological disorders or a history of alcohol or drug abuse, History of allergic reaction to the medications used in the study, Use of other investigational drugs within 30 days prior to the study.

The safety and efficacy parameters were compared with baseline and follow-up data with laboratory investigations, demographics were analyzed in the study. Adverse events / side effects were noted for each follow-up visits.

Ethics Committee Approval

All study related documents Protocol, Case Report Form, Dairy card, Investigator Brochure and Informed Consent Documents (English and Kannada Versions). Written Informed Consent was obtained from the subjects before the start of the trial and after due approval from IEC/IRB. Ethics Committee notifications as per the GCP guidelines issued by Central Drugs Standard Control Organization and Ethical guidelines for biomedical research on human subjects issued by Indian council of Medical Research has been followed during the Conduct of the Study (Clinical IEC-Institutional Ethics Committee for Ethics in Research and Approved on 11 Sep 2018.

Study Outcomes

Primary Outcomes

- Significant Reduction in sign and symptoms chronic bronchitis from baseline to EOT.
- Chest X-ray analysis from baseline to end of treatment.
- Improvement in Immunity
  - Total IgG and total IgM & IgE to see improvement in immunity from baseline to end of treatment

Secondary Outcomes

Safety assessed by Adverse Events

Disposition of Subjects

Total of 40 subjects each group 20 subjects
1. TEST- Curcumin Capsule
2. PLACEBO – Placebo Capsule

The study was planned on 40 patients, i.e., with an ITT (Intension to treat) population of 40 patients. 20 patients in Treatment- A and 20 patients in Treatment- B. All 40 patients completed the study. Efficacy analyses was performed on PP population i.e., FAS (Full Analysis set) of 40 Patients.

Visit Details

The patients were screened and enrolled. The enrollment day was considered as the baseline Day 1 (Randomization, IP Dispensing), Day 14, Day 28, Day 56 (Compliance checking), follow-up visit 5 at 70 days

Statistical Analysis

Statistical Analysis of data obtained after the completion of study was analyzed using SAS software for windows, version 9.1, at 5% level of significance ($\alpha = 0.05$).

The study was planned on 40 patients, i.e., with an ITT (Intension to treat) population of 40 Patient. There was no drop out and / or withdrawn cases in the study so the PP (per protocol) population is also 40 patients. Study was planned in such a way that 40 Patient were allocated to both treatment arms i.e., Test-A & Placebo-B, respectively. Out of 40 patients included in the study 17 females& 23 males took part in the trial.

Efficacy analyses was performed on PP population i.e., FAS (Full Analysis set) of 40 Patient. The primary and secondary parameters considered for efficacy analysis were.

RESULTS

In the study 40 patients were screened and 40 patients were enrolled after meeting the inclusion Criteria and they were randomised randomly into Treatment- A, Treatment- B.

Data Sets Analyzed

Table 1: Data sets analyzed for the test and placebo treatments.

Treatments	Placebo	Test
Enrolled	20	20
Randomized	20	20
No. of patients completed visit	20	20
Withdrawn	0	0

Efficacy Evaluation

Primary Endpoints

1. **Significant Reduction in sign and symptoms of chronic bronchitis from baseline to EOT**

A separate set of analyses were performed to check the efficacy of Test (A) in comparison to Placebo (B) for Baseline and EOT values.

I. Evaluation Of Total Severity Score Of Coughing Between Test (A) & Placebo (B) Comparisons between the coughing scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of coughing scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as <.0001, which shows that there is a statistically significant difference among the scores. Considering Table 05 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 02 and this proves that Test-A is more efficacious in alleviating cough in patients as compared to Placebo-B.

Descriptive statistics of coughing

Descriptive Statistics of Coughing				
Outcome	Test (A)		Placebo (B)	
	Baseline	EOT	Baseline	EOT
Mean value	7.55	2.65	7.70	4.90
Std	1.05	0.99	0.87	0.85
Sem	0.24	0.22	0.19	0.19

Table No 5: Anova for Total Severity Score for coughing between Test (A) & Placebo (B).

Anova for Total severity Score for coughing between Test (A) & Placebo (B)				
Drug Code	Mean Difference	T-Value	P-Value	95% Confidence Interval
Test (A)	-4.90	-6.56	<.0001	(-5.35,-4.44)
Placebo (B)	-2.80			(-3.25,-2.34)
(A-B)	-2.10			(-2.74,-1.45)

Test (A) & Placebo (B)

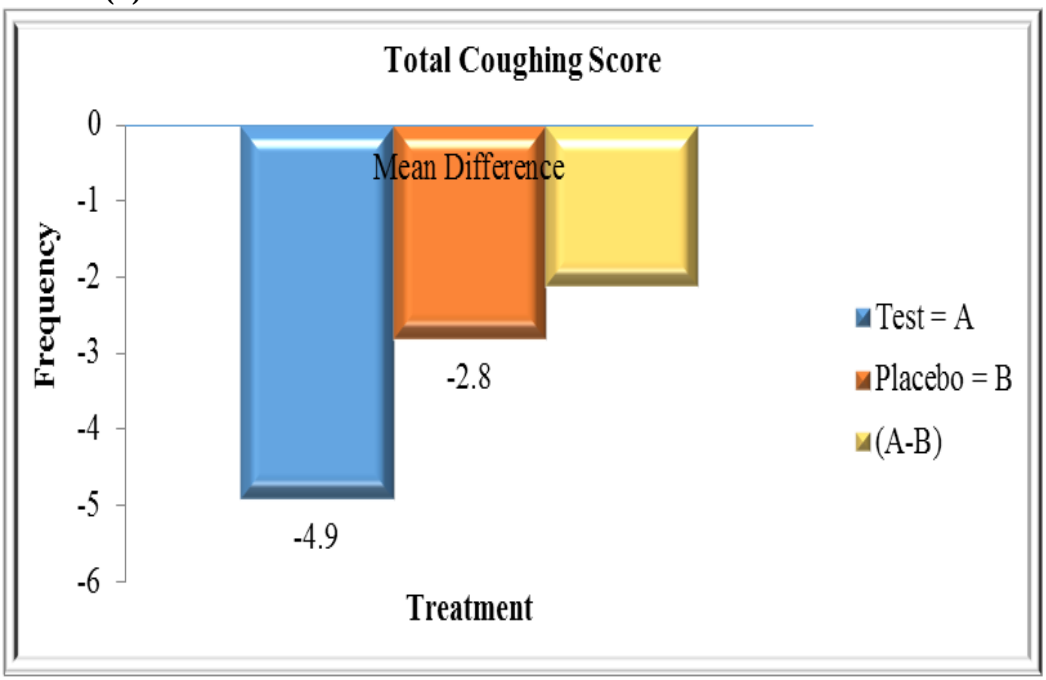


Fig. 02: Total severity Score for coughing between.

II. Evaluation Of Total Severity Score For Mucus Production Between Test (A) & Placebo (B) Comparisons between the Mucus scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of Mucus scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as <.0001, which shows that there is statistically significant difference among the scores. Considering Table 06 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 03 and this proves that Test-A significantly reduces the mucous secretion in patients which gives immense relief as compared to Placebo-B.

Descriptive statistics of Mucus

Descriptive Statistics Of Mucus				
Outcome	**Test (A)**		**Placebo (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	6.10	2.10	5.90	3.55
Std	1.02	0.91	0.85	1.05
Sem	0.23	0.20	0.19	0.24

Table No 6: Anova for Total Severity for Mucus production between Test (A) & Placebo (B).

Anova for Total severity Score of Mucus between TEST(A) & PLACEBO (B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-4.00	-4.71	<.0001	(-4.50, -3.49)
Placebo (B)	-2.35			(-2.85, -1.84)
(A-B)	-1.65			(-2.35, -0.94)

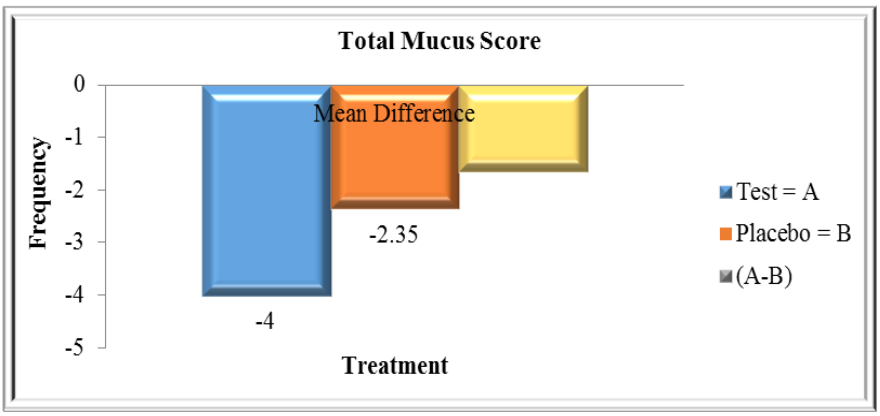


Fig. 03: Total severity Score of Mucus between TEST (A) & PLACEBO (B).

III. Evaluation Of Total Severity Score Of Wheezing Or Whistling Sound Between Test (A) & Placebo (B) Comparisons between the wheezing or whistling sound scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of wheezing or whistling sound scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as 0.0008, which shows that there is statistically significant difference among the scores. Considering Table 07 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 04 and this proves that Test-A is highly efficacious in reduction of wheezing and whizzing sound in patient's as compared to Placebo-B.

Descriptive statistics of wheezing or whistling sound

Descriptive Statistics Of Wheezing Or Whistling Sound				
Outcome	**Test (A)**		**Placebo (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	4.50	3.05	2.55	2.70
Std	2.37	1.40	3.27	2.20
Sem	0.53	0.31	0.73	0.49

Table No 7: Anova for Total Severity Score of wheezing or whistling sound in the lungs between Test (A) & Placebo (B).

ANOVA for Total severity Score of Wheezing or whistling sound in the lungs between TEST (A) & PLACEBO (B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-1.45	-3.64	0.0008	(-2.07, -0.82)
Placebo (B)	0.15			(-0.47, 0.77)
(A-B)	-1.60			(-2.49, -0.70)

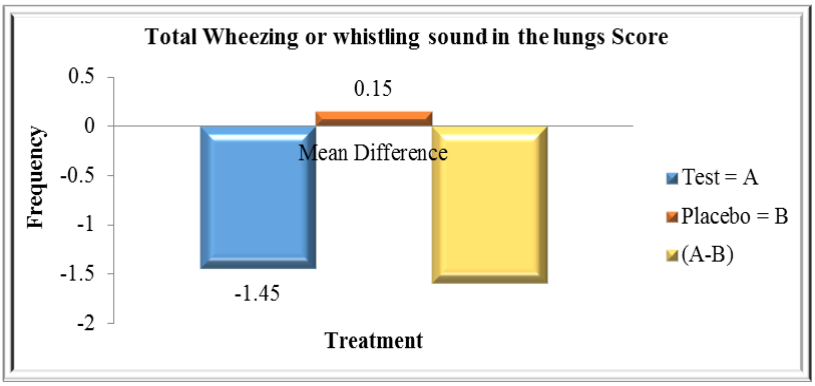


Fig. 04: Total severity Score of wheezing or whistling sound in the lungs between TEST (A) & PLACEBO (B).

IV. Evaluation of Total Severity Score for Low Grade Fever Between Test (A) & Placebo (B) Comparisons between the low fever scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of low fever scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as 0.0001, which shows that there is statistically significant difference among the scores. Considering Table 08 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 05 and this proves that Test-A is more effective in controlling low grade fever in patients compared to Placebo-B.

Descriptive statistics of Low fever.

Descriptive Statistics Of Low Fever				
Outcome	**Test (A)**		**Placebo (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	4.30	1.00	6.05	4.25
Std	1.08	0.00	1.10	0.44
Sem	0.24	0.00	0.25	0.10

Table No 8: ANOVA for Total Severity Score for Low grade fever between TEST (A) & PLACEBO (B).

ANOVA for Total severity Score of Low grade fever between TEST(A) & PLACEBO (B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-3.30	-4.34	0.0001	(-3.79, -2.80)
Placebo (B)	-1.80			(-2.29, -1.30)
(A-B)	-1.50			(-2.19, -0.80)

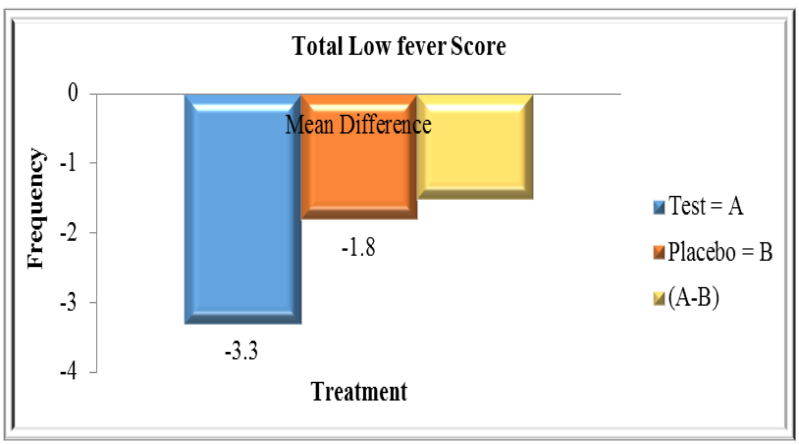


Fig. 05: Total severity Score of Signs and symptoms Low fever between TEST (A) & PLACEBO (B).

V. Evaluation of total severity score for chest discomfort between test (a) & placebo (B) Comparisons between the chest discomfort scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of chest discomfort scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as 0.0006, which shows that there is statistically significant difference among the scores. Considering Table 09 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 06 and this proves that Test-A is more effective in alleviating the symptoms of chest discomfort in patients and this can be correlated with reduction in mucous secretion and cough symptom as compared to Placebo-B.

Descriptive statistics of chest discomfort.

Descriptive Statistics Of Chest Discomfort				
Outcome	**Test (A)**		**Placebo (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	3.70	1.15	1.95	1.60
Std	1.98	0.37	2.48	0.88
Sem	0.44	0.08	0.56	0.20

Table No 9: ANOVA for Total Severity Score of Chest discomfort between TEST (A) & PLACEBO (B).

ANOVA for Total severity Score of Chest discomfort between TEST (A) & PLACEBO (B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-2.55	-3.77	0.0006	(-3.38, -1.71)
Placebo (B)	-0.35			(-1.18, 0.48)
(A-B)	-2.20			(-3.38, -1.01)

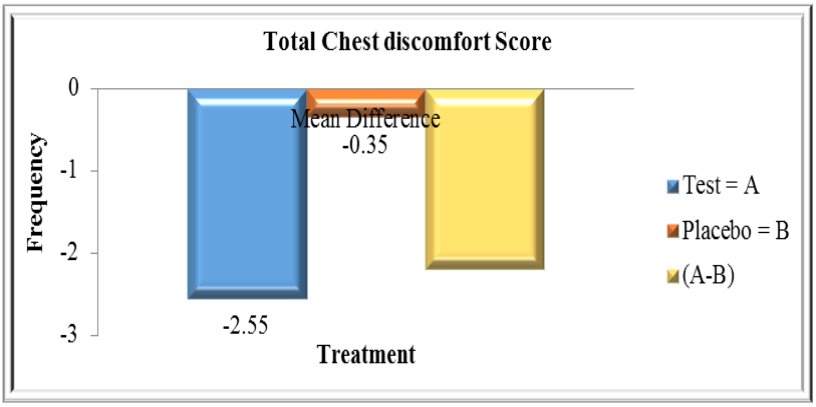


Fig. 06: Total severity Score of by Subjective Chest discomfort between TEST (A) & PLACEBO (B).

VI. Evaluation of total severity score for of shortness of breath between TEST (A) & PLACEBO (B) Comparisons between the shortness of breath scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of shortness of breath scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as 0.0022, which shows that there is statistically significant difference among the scores. Considering Table 10 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 07 and this proves that Test-A is more efficacious in reducing the symptoms as compared to Placebo-B.

Descriptive statistics of shortness of breath

Descriptive statistics of shortness of breath				
Outcome	**TEST (A)**		**PLACEBO (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	3.95	1.20	3.80	1.90
Std	1.00	0.41	0.70	0.72
Sem	0.22	0.09	0.16	0.16

Table No 10: ANOVA for Total Severity Score of Shortness of breath between TEST (A) & PLACEBO (B).

ANOVA for Total severity Score of Shortness of breath between TEST (A) & PLACEBO (B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-2.75	-3.28	0.0022	(-3.12, -2.37)
Placebo (B)	-1.90			(-2.27, -1.52)
(A-B)	-0.85			(-1.37, -0.32)

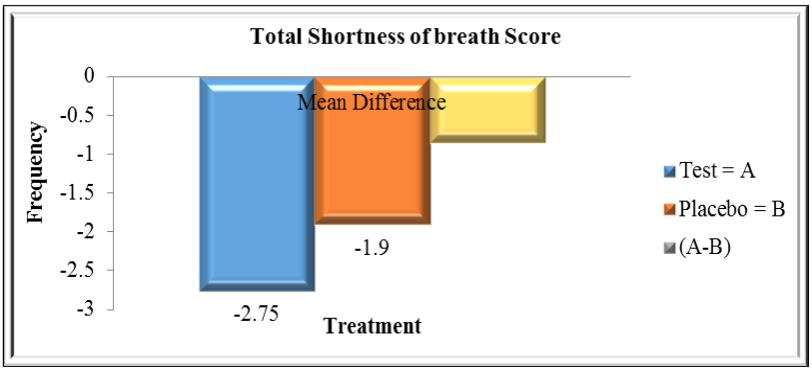


Fig. 07: Total severity Score of Shortness of breath between TEST (A) & PLACEBO (B).

VII. Evaluation of total severity score of cold symptoms between TEST (A) & PLACEBO (B) Comparisons between the cold symptoms scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of cold symptoms scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as <.0001, which shows that there is statistically significant difference among the scores. Considering Table 11 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 08 and this proves that Test-A is more effective in reducing all the symptoms of cold like fatigue, watery eyes and running nose in patient's as compared to Placebo-B.

Descriptive statistics of cold symptoms.

Descriptive Statistics Of Cold Symptoms				
Outcome	**Test (A)**		**Placebo (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	6.65	2.45	6.80	4.75
Std	1.04	0.89	1.06	0.91
Sem	0.23	0.20	0.24	0.20

Table No 11: ANOVA for Total Severity Score of Cold symptoms between TEST (A) & PLACEBO (B).

ANOVA for Total severity Score of Cold symptoms between TEST(A) & PLACEBO (B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-4.20	-6.04	<.0001	(-4.70, -3.69)
Placebo (B)	-2.05			(-2.55, -1.54)
(A-B)	-2.15			(-2.87, -1.42)

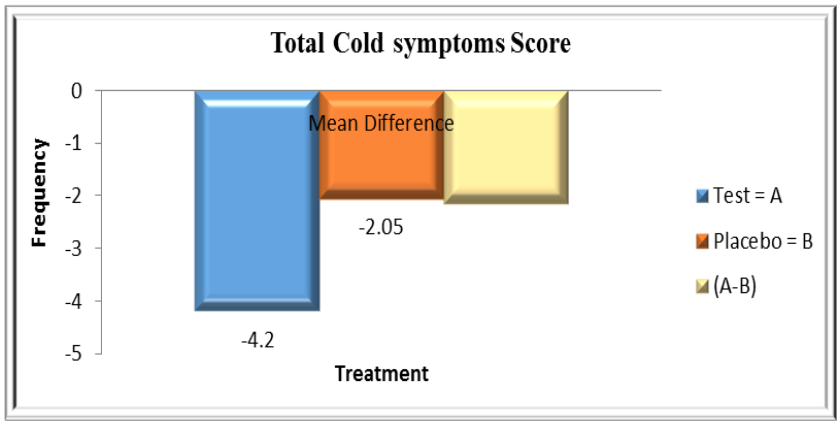


Fig. 08: Total severity Score of Cold symptoms between TEST (A) & PLACEBO (B).

VIII. Evaluation of total severity score for sign and symptoms of frequent respiratory infections between TEST (A) & PLACEBO (B) Comparisons between the frequent respiratory infections scores were done from baseline to EOT using ANOVA for both Test-A and Placebo-B arm, respectively.

For the comparison of Frequent respiratory infections scores from baseline to EOT the p-value was found for "Test-A vs. Placebo-B" as <.0001, which shows that there is statistically significant difference among the scores. Considering Table 12 we can observe that mean change was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been

reflected in Fig. 09 and this proves that Test-A is more efficacious in reducing the episodes of frequent respiratory tract infections before and after treatment as compared to Placebo-B.

Descriptive statistics of frequent respiratory infections.

Descriptive Statistics of Frequent Respiratory Infections				
Outcome	**Test (A)**		**Placebo (B)**	
	Baseline	**EOT**	**Baseline**	**EOT**
Mean value	6.20	2.70	6.15	4.90
Std	0.83	1.22	0.93	0.85
Sem	0.19	0.27	0.21	0.19

Table No 12: ANOVA for Total Severity Score of Signs and symptoms frequent respiratory infections between TEST (A) & PLACEBO (B).

ANOVA for Total severity Score of Signs and symptoms Frequent respiratory infections between TEST(A) & PLACEBO(B)				
Drug Code	**Mean Difference**	**T-Value**	**P-Value**	**95% Confidence Interval**
Test (A)	-3.50	-5.07	<.0001	(-4.13, -2.86)
Placebo (B)	-1.25			(-1.88, -0.61)
(A-B)	-2.25			(-3.14, -1.35)

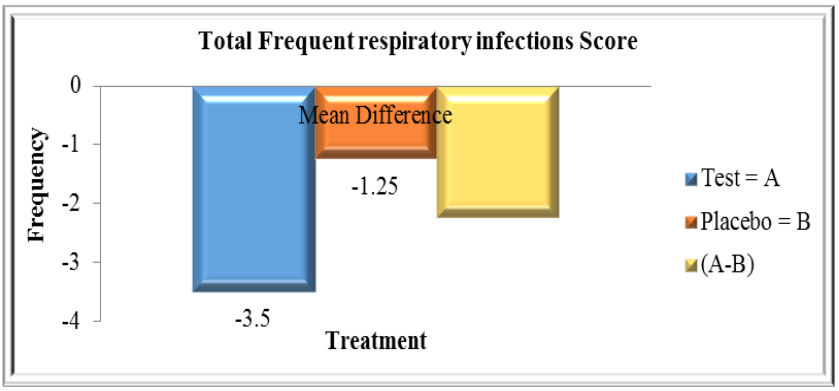


Fig. 09: Total severity Score of Signs and symptoms Frequent respiratory infections between TEST (A) & PLACEBO (B).

IX. Evaluation of total severity score for sign and symptoms of blue skin discoloration between TEST (A) & PLACEBO (B) There were no symptoms reported for the Blue skin discoloration for both Test-A and Placebo-B arm. So we were not able to perform any statistical analysis for this efficacy parameter.

2. Chest X-ray analysis from baseline to end of treatment

Change in chest X-ray score for Test – A & Placebo - B arms were assessed from X-ray reports independently. As per Table 13A, it is evident that, 17 patient's X-ray report was clinically abnormal and 3 patient's X-ray report was normal at Baseline but at the End of Treatment all patient's X-ray reports were normal in Test (A) arm, whereas all 20 patient's X-ray report was abnormal NCS at Baseline but at the End of Treatment only 9 patient's X-ray report were normal in Placebo (B) arm (Table 13B & Fig. 11).

At end of the treatment p-value was found as <.0001 which shows that there is a statistically significant association between Test-A & Placebo-B in comparison to the normal and abnormal events.

Considering Table 13(A), 13(B) & 13(C) we can observe that change in chest X-ray score from X-ray report was more for Test-A arm as compared to Placebo-B arm, respectively and the same has been reflected in Fig. 11. So, this evidences the superiority of Test (A) over Placebo (B).

Table No 13(A): Analysis of Change in Chest X ray findings from Baseline to the EOT (Test = A).

Analysis of Change in Chest X ray findings from Baseline to the EOT (Test = A)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	17	0
Normal	3	20

Table No 13(B): Analysis of Change in Chest X ray findings from Baseline to the EOT (Placebo= B).

Analysis of Change in Chest X ray findings from Baseline to the EOT (Placebo =B B)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	20	11
Normal	0	9

Table No 13(C): Analysis of Change in Chest X ray findings at EOT between Test (A) and Placebo (B).

Analysis of Change in Chest X ray findings at EOT between TEST(A) and PLACEBO(B)			
Outcome	**Abnormal NCS**	**Normal**	**P- value**
Test (A)	0	20	<.0001
Placebo (B)	11	9	

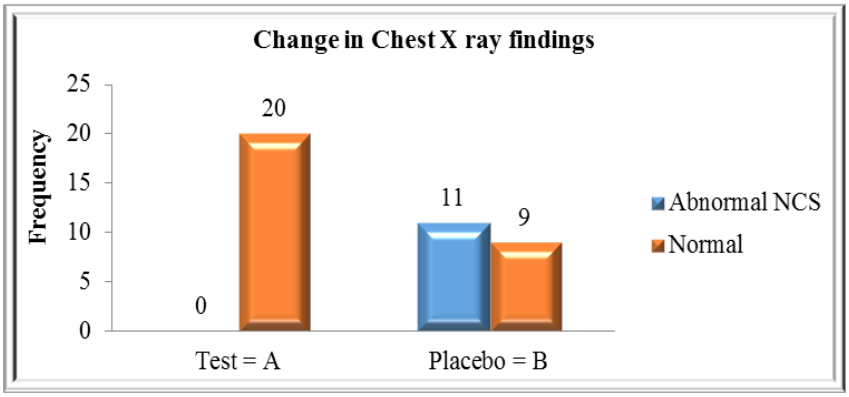


Fig. 10: Analysis of Change in Chest X ray findings at EOT between TEST (A) and PLACEBO (B).

3. Improvement in Immunity (Total IgG, IgM & IgE to see improvement in immunity from baseline to end of treatment)

I. Improvement in Immunity (IgG)

Improvement in Immunity Score of IgG for Test – A & Placebo - B arms were assessed from lab report independently. As per Table 14A, it is evident that, 9 patient's Immunity report of IgG was clinically abnormal and 11 patient's Immunity report of IgG was normal at Baseline but at the End of Treatment all patient's Immunity report of IgG were normal in Test (A) arm, whereas 12 patient's Immunity report of IgG was abnormal NCS at Baseline but at End of Treatment only 8 patient's Immunity report of IgG were normal in Placebo (B) arm (Table 14B & Fig.12).

At end of the treatment p-value was found as <.0001 which shows that there is statistically significant association between Test-A & Placebo-B in comparison to the normal and abnormal events.

Considering Table 14(A), 14(B) & 14(C) we can observe that improvement in patient's immunity (IgG) was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 12. So, this evidences the superiority of Test (A) over Placebo (B).

Table No 14(A): Improvement in Immunity (IgG) from Baseline to the EOT (Test= A).

Improvement in Immunity(IgG) (Test = A)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	9	0
Normal	11	20

Table No 14(B): Improvement in Immunity (IgG) from Baseline to the EOT (Placebo= B).

Improvement in Immunity(IgG) (Placebo = B)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	12	12
Normal	8	8

Table No 14(C): Improvement in Immunity (IgG) at EOT between TEST (A) and PLACEBO (B).

Improvement in Immunity(IgG) at EOT between TEST(A) and PLACEBO(B)			
Outcome	**Abnormal NCS**	**Normal**	**P- value**
Test (A)	0	20	<.0001
Placebo (B)	12	8	

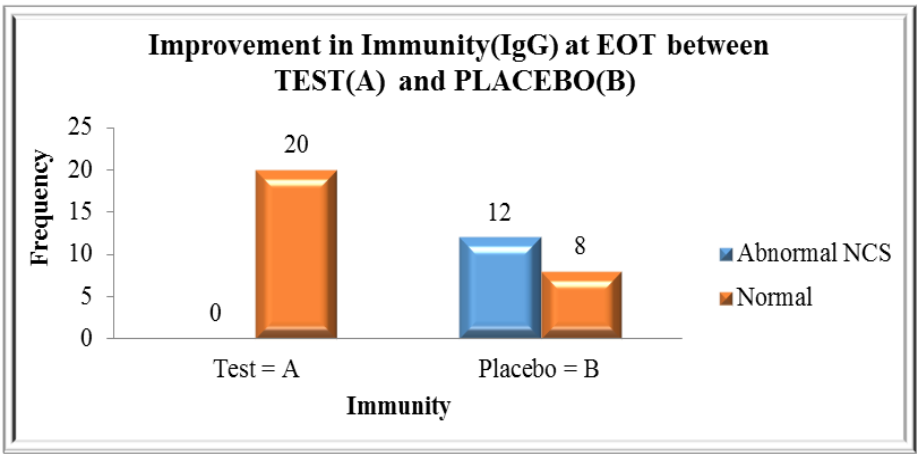


Fig. 11: Improvement in Immunity (IgG) at EOT between TEST (A) and PLACEBO (B).

II. Improvement in Immunity (IgM)

Improvement in Immunity Score of IgM for Test – A & Placebo - B arms were assessed from lab report independently. As per Table 15A, it is evident that, 12 patient's Immunity report of IgM was clinically abnormal and 8 patients Immunity report of IgM was normal at Baseline but at the End of Treatment all patient's Immunity report of IgM were normal in Test (A) arm, whereas 10 patient's Immunity report of IgM was abnormal NCS at Baseline but at the End of Treatment only 10 patient's Immunity report of IgM were normal in Placebo (B) arm (Table 15B & Fig. 13).

At end of the treatment p-value was found as 0.0003 which shows that there is statistically significant association between Test-A & Placebo-B in comparison to the normal and abnormal events.

Considering Table 15(A), 15(B) & 15(C) we can observe that improvement in patient's immunity (IgM) was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 13. So, this evidences the superiority of Test (A) over Placebo (B).

Table No 15(A): Improvement in Immunity (IgM) from Baseline to the EOT (Test= A).

Improvement in Immunity(IgM) (Test = A)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	12	0
Normal	8	20

Table No 15(B): Improvement in Immunity (IgM) from Baseline to the EOT (Placebo= B).

Improvement in Immunity(IgM) (Placebo = B)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	10	10
Normal	10	10

Table no 15(C): Improvement in Immunity (IgM) at EOT between TEST (A) and PLACEBO (B)

Improvement in Immunity(IgM) at EOT between TEST(A) and PLACEBO(B)			
Outcome	**Abnormal NCS**	**Normal**	**P- value**
Test = A	0	20	0.0003
Placebo = B	10	10	

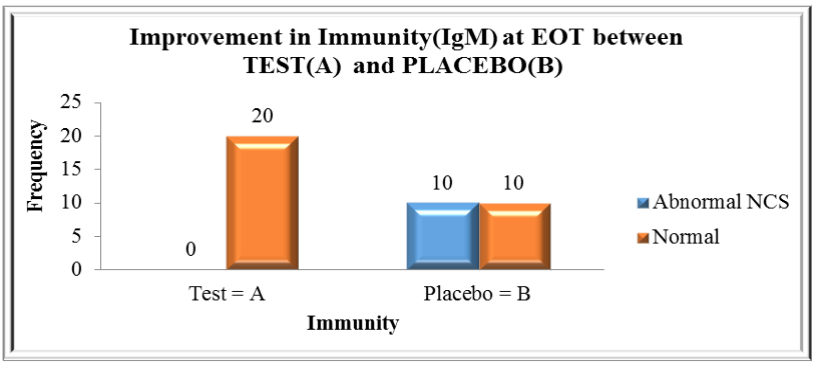


Fig. 12: Improvement in Immunity (IgM) at EOT between TEST (A) and PLACEBO (B).

III. Improvement in Immunity (IgE)

Improvement in Immunity Score of IgE for Test – A & Placebo - B arms were assessed from lab report independently. As per Table 17A, it is evident that, 7 patients Immunity report of IgE was clinically abnormal and 13 patients Immunity report of IgE was normal at

Baseline but at the End of Treatment all patient's Immunity report of IgE were normal in Test (A) arm, whereas 12 patient's Immunity report of IgE was abnormal NCS at Baseline but at End of Treatment only 9 patient's Immunity Score of IgE were normal in Placebo (B) arm (Table 17B & Fig.14).

At end of the treatment p-value was found as <.0001 which shows that there is statistically significant association between Test-A & Placebo-B in comparison to the normal and abnormal events.

Considering Table 17(A), 17(B) & 17(C) we can observe that improvement in patient's immunity (IgE) was more for Test-A arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 14. So this proves the efficacy of Test (A) over Placebo (B).

Table No 16 (A): Improvement in Immunity (IgE) from Baseline to the EOT (Test= A).

Improvement in Immunity(IgE) (Test = A)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	7	0
Normal	13	20

Table No 16(B): Improvement in Immunity (IgE) from Baseline to the EOT (Placebo= B).

Improvement in Immunity(IgE) (Placebo = B)		
Outcome	**Baseline**	**EOT**
Abnormal NCS	12	11
Normal	8	9

Table 16 (C): Improvement in Immunity (IgE) at EOT between TEST (A) and PLACEBO (B)

Improvement in Immunity(IgE) at EOT between TEST(A) and PLACEBO(B)			
Outcome	**Abnormal NCS**	**Normal**	**P- value**
Test = A	0	20	<.0001
Placebo = B	11	9	

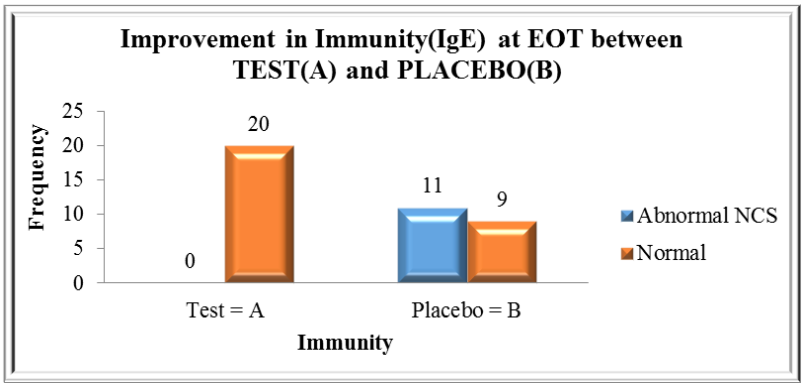


Fig No 13: Improvement in Immunity (IgE) at EOT between TEST (A) and PLACEBO (B).

Secondary Endpoints

Safety analysis was done as per the ADVERSE EVENTS reported No AEs/ADR was reported which was related to study drug which confirmed that TEST drug is safe to be given in human population.

There were 02 (Patient No; 01-009, 01-032) adverse event was observed during the study, which was resolved and not related to study drug.

The detail list of adverse events mentioned as follow:

Sub. No	Name of AE	SAE	Onset date	Resolved date	Intensity	Causality	Action Taken	Outcome of the events
01-009	Hypertension	No	09 Feb 2019	11 Feb 2019	Mild	Unlikely	Tab. Amlodepin 5mg	Resolved
01-032	Hypertension	No	15 Apr 2019	17 Apr 2019	Mild	Unlikely	Tab. Metaprolol 50 mg	Resolved

DISCUSSION AND CONCLUSION

Bronchitis is a term that describes inflammation of the bronchial tubes (bronchi and the smaller branches termed bronchioles) that results in excessive secretions of mucus into the tubes, leading to tissue swelling that can narrow or close off bronchial tubes.

There are several clinical trials which proves that curcumin has an anti-inflammatory effect by lowering histamine levels and by possibly increasing the production of natural cortisone by adrenal glands additionally. The mechanism of action by which curcumin shows anti-inflammatory effect is also by attenuating inflammatory response of TNF-α stimulated human endothelial cells by interfering with NF-κB. Furthermore, curcumin is also capable of preventing platelet-derived growth factor (PDGF).

This study was done on 40 patients with chronic bronchitis. Patients were selected as per the inclusion

criteria. It was a double blinded study where patients were allocated into 2 arms PLACEBO and TEST arm as per the randomization chart generated.

Efficacy analysis was performed on all 40 patients who completed the trial. The results obtained from Intra-Group statistical analyses and Efficacy analyses of primary endpoints between the TEST and PLACEBO showed statistically significant improvement in symptoms of chronic bronchitis and also improving the immunity of patients in TEST (CURCUMIN) arm.

Safety analysis was done as per the ADVERSE EVENTS reported. Two AEs which was not related to TEST drug was reported which confirmed that TEST drug is safe to be given in human population.

The study concludes that, TEST (CURCUMIN) due to its anti-inflammatory and immunomodulatory effect it is more efficacious and safer in comparison to PLACEBO (B) in treatment of cough due to chronic bronchitis and also alleviating the symptoms of chronic bronchitis along with improvement in immunity.

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