Clinical Research

KEYWORDS: non-steroidal anti-inflammatory drugs (NSAIDs), Rheumatoid Arthritis (RA) and cyclooxygenase (COX)

A CLINICAL STUDY TO EVALUATE THE EFFICACY & SAFETY OF CURCUVAIL IN PATIENT WITH CHRONIC JOINT PAIN (RHEUMATOID ARTHRITIS).

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ABSTRACT:-

Background

Rheumatoid Arthritis is a systemic inflammatory and destructive joint disease with a prevalence of about 1–2% of the adult population worldwide. Rheumatoid Arthritis (RA) is an autoimmune disease that can cause joint pain and damage throughout body. It typically results in warm, swollen, and painful joints.

The major goal of Rheumatoid Arthritis treatment is to reduce joint pain induced by inflammation in the joints, daily wear and tear of joints, and muscle strains. The existing pharmaceuticals for treating Rheumatoid Arthritis are analgesics, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs), which reduce the symptoms such as severe pain and inflammation. Classical NSAIDs are cyclooxygenase (COX) inhibitors that inhibit prostaglandin and thromboxane synthesis, thereby reducing inflammation. New NSAIDs selectively inhibit COX-2 and are usually specific to inflamed tissue, which decreases the risk of peptic ulcer.

The Curcuminoid are natural phenols that are responsible for the yellow color of turmeric. Curcumin can exist in several tautomeric forms, including a 1, 3-diketo form and two equivalent enol forms. The present study is conducted to evaluate safety and efficacy of Curcumin in Patients with Chronic joint pain (Rheumatoid Arthritis).

Objectives

To assess the efficacy and safety of Curcumin in Patients with Chronic joint pain (Rheumatoid Arthritis).

Conclusion:

The study concludes that, TEST -CURCUVAIL (CURCUMIN) due to its anti-inflammatory and immunomodulatory effect it is more efficacious and safer in comparison to PLACEBO (B) in treatment of chronic joint pain due to rheumatoid arthritis.

INTRODUCTION

Rheumatoid Arthritis

The term Rheumatoid Arthritis is derived from the Greek words “artho” and “itis,” meaning joint and inflammation, respectively. Rheumatoid Arthritis is a form of joint disorder characterized by chronic inflammation in one or more joints that usually results in pain and is often disabling. Rheumatoid Arthritis includes more than 100 different forms: the most common form is osteoarthritis, but other forms include rheumatoid Arthritis, psoriatic Rheumatoid Arthritis, and related autoimmune diseases. Although the causes of these diseases are different, their symptoms and treatments are similar. The worldwide prevalence of knee osteoarthritis increased 26.6% from 1990 to 2010, and it affects about 9.6% of men and 18% of women more than 60 years of age. Rheumatoid Arthritis is a systemic inflammatory and destructive joint disease with a prevalence of about 1–2% of the adult population worldwide. Rheumatoid Arthritis (RA) is an autoimmune disease that can cause joint pain and damage throughout body. It typically results in warm, swollen, and painful joints.

The major goal of Rheumatoid Arthritis treatment is to reduce joint pain induced by inflammation in the joints, daily wear and tear of joints, and muscle strains. The existing pharmaceuticals for treating Rheumatoid Arthritis are analgesics, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs), which reduce the symptoms such as severe pain and inflammation. Classical NSAIDs are cyclooxygenase (COX) inhibitors that inhibit prostaglandin and thromboxane synthesis, thereby reducing inflammation. New NSAIDs selectively inhibit COX-2 and are usually specific to inflamed tissue, which decreases the risk of peptic ulcer.

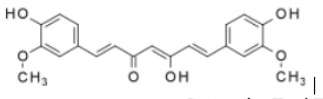
However, their long-term use cannot be sustained due to inadequate pain relief, immune disturbances, and cardiovascular adverse events.

Therefore, herbal therapies with anti-inflammatory properties and minimum side effects are needed for the treatment of Rheumatoid Arthritis, including rheumatoid Arthritis and osteoarthritis. The purpose of this study is to systemically evaluate randomized clinical trials (RCTs) of Curcumin for treating Rheumatoid Arthritis symptoms.

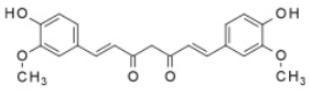
DESCRIPTION

Curcumin (8, 9)

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 C21H20O6 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 color 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 show that the efficacy of Curcumin in Patients with Chronic joint pain (Rheumatoid Arthritis).

Secondary Objective:

To evaluate the safety of Curcumin in Patients with Chronic joint pain (Rheumatoid Arthritis).

METHODS:-

Inclusion Criteria:-

Men and women with age of 40 – 65 with a diagnosed Rheumatoid Arthritis from last 3 month, willing to give written informed consent, able to visit the medical institutions throughout the study period, Patient have not participated in a similar investigation in the past 3 month.

Exclusion Criteria:-

Patient with Uncontrolled hypertension or diabetes, Hepatic or renal impairment, Patient with Current or expected use of anticoagulant, patients for imminent joint replacement, Diagnosis of gastric or duodenal ulceration and/or history of significant gastro-duodenal bleeding, within the last 6 months, Participation within 30 days prior to screening in another investigational study, Conditions in the opinion of the investigator make the subject unsuitable to participate in the study such as , any serology positive, Pregnant (or) Lactating, Previous history of allergic reaction to Curcumin.

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 02 Nov 2018.

Study Outcomes:-

Primary Outcomes:-

- Improvement in the PGIC scale (Patient global impression of change) and quality of life.
- Improvement in Signs and symptoms as per investigator's examination.
- Changes in the Rheumatoid Arthritis impact measurement scale (AIMS 2)
- Change from Baseline in the CGI (Clinical Global Impression) scale score
- X-ray & Anti-CCP (anti-cyclic citrullinated peptide) TEST CURCUVAIL result analysis

Secondary Outcomes:-

- Safety assessed by Adverse Events
- Patient questionnaire

Disposition of Subjects:-

Total of 30 subjects each group 15 subjects
1. TEST -CURCUVAIL- Curcumin Capsule
2. PLACEBO – Placebo Capsule

The study was planned on 30 patients, i.e., with an ITT (Intension to treat) population of 30 patients. 15 patients in Treatment- A and 15 patients in Treatment- B. All 30 patients completed the study. Efficacy analyses was performed on PP population i.e., FAS (Full Analysis set) of 30 Patients.

Visit Details:-

The patients were screened and enrolled. The enrollment day was considered as the baseline Day 1 (Randomization, IP Dispensing), Day 30, Day 60 (Compliance checking), follow-up visit 4 at 90 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 30 patients, i.e., with an ITT (Intension to treat) population of 30 patients. There was no drop out and / or withdrawn cases in the study so the PP (per protocol) population is also 30 patients. Study was planned in such a way that 30 patients were allocated to both treatment arms i.e., 15 patients in Placebo-A and 15 patients in TEST -CURCUVAIL-B. Out of 30 patients included in the study 26 were females and 4 were males.

Efficacy analyses was performed on PP population i.e., FAS (Full Analysis set) of 30 patients. The primary and secondary parameters considered for efficacy analysis were:

RESULTS:-

In the study 30 patients were screened and 30 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 -CURCUVAIL and placebo treatments

Treatments	Placebo	TEST -CURCUVAIL
Enrolled	15	15
Randomized	15	15
No. of patient completed visit	15	15
Withdrawn	0	0

Efficacy Evaluation

I. Improvement in the PGIC scale (Patient' global impression of change) and QOL from baseline to EOT

Comparisons between the total score of improvement in the PGIC Scale were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo -A arm, respectively.

For the comparison of the improvement in the PGIC Scale score from baseline to EOT the p-value was found to be as 0.0008 for TEST -CURCUVAIL-B vs. Placebo-A, which shows that there is statistically significant difference among the scores. Considering Table 06 we can observe that mean change was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 02 and this proves that TEST -CURCUVAIL-B is more efficacious in overall improvement of Quality of life, reduction in symptoms and reduction in restricted mobility in patients in comparison to Placebo -A.

Table 02: Descriptive statistics of PGIC scale

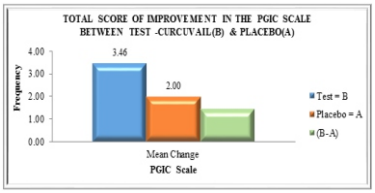
DESCRIPTIVE STATISTICS OF PGIC				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	1.13	4.60	1.07	3.07
STD	0.35	1.45	0.26	0.59
SEM	0.09	0.38	0.07	0.15

Table 03: ANOVA for Score of Improvement in the PGIC scale for TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -CURCUVAIL = B	3.47	3.7700	0.0008	(2.90, 4.02)
Placebo = A	2.00			(1.43, 2.56)
(B-A)	1.47			(0.67, 2.26)

Fig. 01 –Score of Improvement in the PGIC scale for TEST -

CURCUVAIL (B) & Placebo (A)



II. Improvement in Signs and symptoms as per investigator examination from baseline to EOT

1. Evaluation of Improvement in the Signs and Symptoms of Tenderness as Per Investigator Examination between TEST -CURCUVAIL (B) & Placebo (A).

Comparisons between the Tender scores were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo-A arm, respectively.

For the comparison of Tender scores from baseline to EOT the p-value was found for "TEST -CURCUVAIL-B vs. Placebo-A" as <.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 -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 03 and this proves that TEST -CURCUVAIL-B is more efficacious in reducing the joint pain and tenderness in rheumatoid arthritis patients in comparison to Placebo-A.

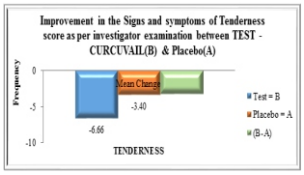
Table 04: Descriptive statistics of Tenderness

DESCRIPTIVE STATISTICS OF TENDERNESS				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	7.87	1.20	8.40	5.00
STD	0.35	0.41	0.51	0.00
SEM	0.09	0.11	0.13	0.00

Table 05: ANOVA for Improvement in the Signs and symptoms of Tenderness score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -CURCUVAIL = B	-6.66	-15.84	<.0001	(-6.96, -6.36)
Placebo = A	-3.40			(-3.69, -3.10)
(B-A)	-3.26			(-3.68, -2.84)

Fig. 02 – Improvement in the Signs and symptoms of Tenderness score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)



2. Evaluation of improvement in the signs and symptoms of warmth as per investigator examination between TEST -CURCUVAIL (b) & placebo (a)

Comparisons between the Warm scores were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo-A arm, respectively.

For the comparison of Warm scores from baseline to EOT the p-value was found for TEST -CURCUVAIL-B vs. Placebo-A as <.0001 which shows that there is statistically significant difference among the scores. Considering Table 10 we can observe that mean change was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 04 and this proves that TEST -CURCUVAIL-B is more efficacious in reducing the warmth of affected joint in comparison to Placebo-A.

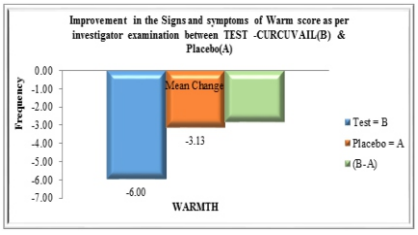
Table 06: Descriptive statistics of frequent Warmth

DESCRIPTIVE STATISTICS OF WARMTH				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	7.87	1.87	8.13	5.00
STD	0.74	0.35	0.64	0.00
SEM	0.19	0.09	0.17	0.00

Table 7: ANOVA for Improvement in the Signs and symptoms of Warmth score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -CURCUVAIL = B	-6.00	-10.47	<.0001	(-6.39, -5.60)
Placebo = A	-3.13			(-3.52, -2.73)
(B-A)	-2.87			(-3.42, -2.30)

Fig. 03 – Improvement in the Signs and symptoms of Warmth score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)



3. Evaluation of improvement in the signs and symptoms of joints swelling score as per investigator examination between TEST -CURCUVAIL (b) & placebo (a)

Comparisons between the Swollen Joints scores were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo-A arm, respectively.

For the comparison of Swollen Joints scores from baseline to EOT the p-value was found for "TEST -CURCUVAIL-B vs. Placebo-A" 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 -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 05 and this proves that TEST -CURCUVAIL-B is more efficacious in alleviating the signs and symptoms of joint inflammation in comparison to Placebo-A.

Table 8: Descriptive statistics of Swollen Joints

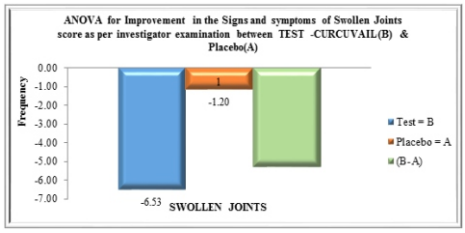
DESCRIPTIVE STATISTICS OF SWOLLEN JOINTS				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	7.93	1.40	7.53	6.33
STD	0.80	0.51	0.52	1.72
SEM	0.21	0.13	0.13	0.44

Table 9: ANOVA for Improvement in the Signs and symptoms of Swollen Joints score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -CURCUVAIL = B	-6.53	-10.50	<.0001	(-7.26, -5.79)

Placebo = A	-1.20			(-1.93, -0.46)
(B-A)	-5.33			(-6.37, -4.29)

Fig. 05 – Improvement in the Signs and symptoms of Swollen Joints score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)



4. Evaluation of improvement in the signs and symptoms of fatigue score as per investigator examination between TEST -CURCUVAIL (b) & placebo (a)

Comparisons between the Fatigue scores were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo-A arm, respectively.

For the comparison of Fatigue scores from baseline to EOT the p-value was found for TEST -CURCUVAIL-B vs. Placebo-A as <.0001 which shows that there is statistically significant difference among the scores. Considering Table 14 we can observe that mean change was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 06 and this proves that TEST -CURCUVAIL-B is more efficacious in reduction of fatigue and thereby improving the patients wellbeing in comparison to Placebo-A.

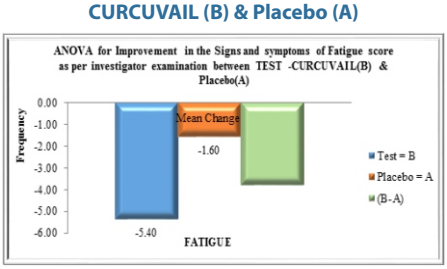
Table 10: Descriptive statistics of Fatigue

DESCRIPTIVE STATISTICS OF FATIGUE				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	6.40	1.00	6.60	5.00
STD	1.55	0.00	1.55	0.00
SEM	0.40	0.00	0.40	0.00

Table 11: ANOVA for Improvement in the Signs and symptoms of Fatigue score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -	-5.40	-6.72	<.0001	(-6.21, -4.58)
Placebo = A	-1.60			(-2.41, -0.78)
(B-A)	-3.80			(-4.95, -2.64)

Fig. 06 – Improvement in the Signs and symptoms of Fatigue score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)



5. Evaluation of improvement in the signs and symptoms of weight loss score as per investigator examination between TEST -CURCUVAIL (b) & placebo (a)

Comparisons between the Weight loss scores were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo-A arm, respectively.

For the comparison of Weight loss scores from baseline to EOT the p-value was found for TEST -CURCUVAIL-B vs. Placebo-A as 0.1534which shows that there is no statistically significant difference among the scores.

Considering Table 16 we can observe that no change for TEST -CURCUVAIL-B arm and some changes were observed for Placebo-A arm, same has been reflected in Fig. 07.

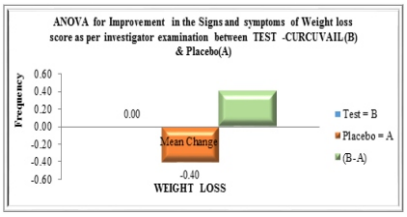
Table 12: Descriptive statistics of Weight loss

DESCRIPTIVE STATISTICS OF WEIGHT LOSS				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	5.00	5.00	5.40	5.00
STD	0.00	0.00	1.06	0.00
SEM	0.00	0.00	0.27	0.00

Table 13: ANOVA for Improvement in the Signs and symptoms of Weight loss score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -CURCUVAIL = B	0.00	1.47	0.1534	(-0.394,0.394)
Placebo = A	-0.40			(-0.794, -0.005)
(B-A)	0.40			(-0.158,0.958)

Fig. 07 – Improvement in the Signs and symptoms of Weight loss score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)



6. Evaluation of improvement in the signs and symptoms of joint stiffness that is usually worse in the morning and after activity score as per investigator examination between TEST -CURCUVAIL (B) & placebo (A)

Comparisons between the Joint stiffness that is usually worse in the morning and after activity scores were done from baseline to EOT using ANOVA for both TEST -CURCUVAIL-B and Placebo-A arm, respectively.

For the comparison of Joint stiffness that is usually worse in the morning and after activity scores from baseline to EOT the p-value was found for TEST -CURCUVAIL-B vs. Placebo-A as <.0001which shows that there is statistically significant difference among the scores. Considering Table 18 we can observe that mean change was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 08 and this proves that TEST -CURCUVAIL-B is more efficacious in improving the joint mobility thereby reducing the stiffness and restricted mobility of the affected joints in comparison to Placebo-A.

Table 14: Descriptive statistics of Joint stiffness that is usually worse in the morning and after activity

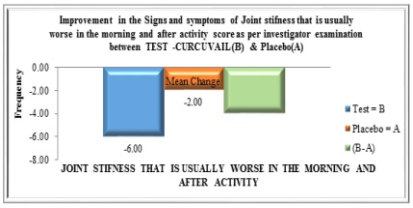
DESCRIPTIVE STATISTICS OF JOINT STIFNESS THAT IS USUALLY WORSE IN THE MORINING AND AFTER ACTIVITY				
OUTCOME	TEST -CURCUVAIL (B)		PLACEBO (A)	
	Baseline	EOT	Baseline	EOT
MEAN VALUE	7.80	1.80	8.53	6.53
STD	1.27	1.01	0.92	1.77

SEM	0.33	0.26	0.24	0.46

Table 15: ANOVA for Improvement in the Signs and symptoms of Joint stiffness that is usually worse in the morning and after activity score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)

Drug Code	Mean Change	T-Value	P-Value	95% Confidence Interval
TEST -CURCUVAIL = B	-6.00	-6.40	<.0001	(-6.90, -5.09)
Placebo = A	-2.00			(-2.90, -1.09)
(B-A)	-4.00			(-5.28, -2.71)

Fig. 08 – Improvement in the Signs and symptoms of Joint stiffness that is usually worse in the morning and after activity score as per investigator examination between TEST -CURCUVAIL (B) & Placebo (A)



III. Changes in the Rheumatoid Arthritis impact measurement scale (AIMS 2)

Frequency distribution was used to compile the scores with their interpretations for Questionnaires of Rheumatoid Arthritis impact by AIMS2 measurement scale. As the entire data was categorical so the frequency distribution for all the variables were drawn for baseline visit and EOT, respectively for the TEST -CURCUVAIL-B and Placebo-A product.

All the questionnaires in AIMS2 Scale measure the overall wellbeing of the patients before and after treatment. Overall wellbeing was measured by reduction in symptoms of joint swelling and restricted mobility of joints.

It was clearly evident from the analysis of 26 questioners in the scale that significant improvement in signs and symptoms of joint swelling are there in the TEST -CURCUVAIL arm compared to placebo arm. This is evident from the responses of patients to the questioners.

So, taking up all considerations into account it's clearly evident that impact on Rheumatoid Arthritis disease activity is found more effective for TEST -CURCUVAIL (B) as compared to Placebo (A).

II. Change from Baseline in the CGI (Clinical Global Impression) scale score

1. Severity of Illness

Changes in Severity of Illness or TEST -CURCUVAIL – B & Placebo - A arms were assessed from CGI scale score independently. As per Table 16 A, it is evident that, at the baseline visit out of 15 patient, 5 patient Markedly ill, 2 Moderately ill& 8 Severely ill but at the EOT,10patient Mildly ill, only 1patients Moderately ill and 4 patient were reported as Normal or not at all ill for TEST -CURCUVAIL(B) arm. Whereas at the baseline visit out of 15 patient,2 patient Markedly ill, 1 patients Moderately ill, 12patient Severely ill but at the EOT, 5 patient Markedly ill, 4 patient Mildly ill, 5patient Moderately ill and only 1 patients were reported as Normal not at all ill for Placebo (A) arm(Table 16 B & Fig.9).

At end of the treatment p-value was found as 0.0073, which shows that there is statistically significant association between TEST -CURCUVAIL-B & Placebo-A in comparison to severity of illness.

Considering Table 16(A), 16(B) & 16(C)we can observe that reduction of Severity of Illness of rheumatoid arthritis was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 9.So this proves the efficacy of TEST -CURCUVAIL (B) over Placebo (A).

Table 16(A): Change in Severity of Illness from Baseline to the EOT (TEST -CURCUVAIL = B)

Change in Severity of Illness from Baseline to the EOT (TEST -CURCUVAIL = B)		
Outcome	Baseline	EOT
Normal	0	4
Mildly ill	0	10
Moderately ill	2	1
Markedly ill	5	0
Severely	8	0

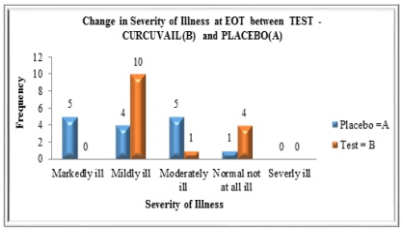
Table 16(B): Change in Severity of Illness from Baseline to the EOT (Placebo = A)

Change in Severity of Illness from Baseline to the EOT (Placebo = A)		
Outcome	Baseline	EOT
Normal	0	1
Mildly ill	0	4
Moderately ill	1	5
Markedly ill	2	5
Severely	12	0

Table 16 ©: Change in Severity of Illness at EOT between TEST -CURCUVAIL (B) and PLACEBO (A)

Change in Severity of Illness at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)			
Outcome	Placebo =A	TEST -CURCUVAIL = B	P-Value
Normal	1	4	0.0073
Mildly ill	4	10	
Moderately ill	5	1	
Markedly ill	5	0	
Severely	0	0	
Total	15	15	

Fig. 9 – Change in Severity of Illness at EOT between TEST -CURCUVAIL (B) and PLACEBO (A)



v Global Improvement

Changes in Global Improvement for TEST -CURCUVAIL – B & Placebo - A arms were assessed from CGI scale score independently. As per Table 17 (A), it is evident that, at the baseline visit out of 15 patient, 3 patient Minimally worse & 12patientMuch worse but at the EOT only 1patientsMinimally worse, 4patientMuch improved, only 1patientsNo change, 2patientVery much worse& 7patientminimally improved were reported for TEST -CURCUVAIL (B) arm.

Whereas at the baseline visit out of 15 patient,7patient Minimally worse, 7patientMuch worse &only 1patientsVery much worse but at the EOT, 2patientMinimally worse, 2patientMuch worse, 8patientNo change and 3patientminimally improved were reported for Placebo (A) arm(Table 17B & Fig.10).

At end of the treatment p-value was found as 0.0089, which shows

that there is statistically significant association between TEST - CURCUVAIL-B & Placebo-A in comparison to Global Improvement. Considering Table 17 (A), 17 (B) & 17 (C) we can observe that Global Improvement was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 10.So this proves the efficacy of TEST -CURCUVAIL (B) over Placebo (A) in overall improvement of disease condition and patients well-being before and after taking the medicine.

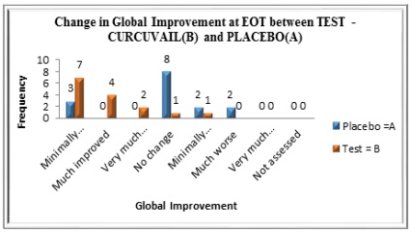
Table 17(A): Change in Severity of Global Improvement from Baseline to the EOT (TEST -CURCUVAIL = B)

Change in Global Improvement from Baseline to the EOT (TEST - CURCUVAIL = B)		
Outcome	Baseline	EOT
Minimally improved	0	7
Much improved	0	4
Very much improved	0	2
No change	0	1
Minimally worse	3	1
Much worse	12	0
Very much worse	0	0
Not assessed	0	0

Table 17 (B): Change in Severity of Global Improvement from Baseline to the EOT (Placebo = A)

Change in Global Improvement at EOT between TEST - CURCUVAIL(B) and PLACEBO(A)			
Outcome	Placebo =A	TEST - CURCUVAIL = B	P-Value
Minimally improved	3	7	0.0089
Much improved	0	4	
Very much improved	0	2	
No change	8	1	
Minimally worse	2	1	
Much worse	2	0	
Very much worse	0	0	
Not assessed	0	0	
Total	15	15	

Fig. 10 – Change in Global Improvemental EOT between TEST - CURCUVAIL (B) and PLACEBO (A)



VI. Efficacy Index (Therapeutic Effect)

Changes in Therapeutic Effect for TEST -CURCUVAIL – B & Placebo - A arms were assessed from CGI. As per Table 73A, it is evident that, at the baseline visit out of 15 patient, only 1patientsMinimal, 5patient Moderate & 9patientUnchanged or worse but at the EOT,9patientMarked, 5patientMinimal &only 1patients Moderate were reported for TEST -CURCUVAIL (B) arm.

Whereas at the baseline visit out of 15 patient, only 1patientsMarked, 3patientMinimal, 3patientModerate& 8 patient Unchanged or worse but at the EOT, only 1patientsMarked, 7patientMinimal, 3patientModerate&4patientUnchanged or worse were reported for Placebo (A) arm(Table 18B & Fig.11).

At end of the treatment p-value was found as 0.0084, which shows that there is statistically significant association between TEST - CURCUVAIL-B & Placebo-A in comparison to Therapeutic Effect.

Considering Table 18 (A), 18(B) &18(C) we can observe that Therapeutic Effect was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 11.So this proves the efficacy of TEST - CURCUVAIL (B) over Placebo (A) in proving the efficacy of the drug.

Table 18(A): Change in Severity of Therapeutic Effect from Baseline to the EOT (TEST -CURCUVAIL = B)

Change in Efficacy Index (Therapeutic Effect) from Baseline to the EOT (TEST -CURCUVAIL = B)		
Outcome	Baseline	EOT
Marked	0	9
Minimal	1	5
Moderate	5	1
Unchanged or worse	9	0

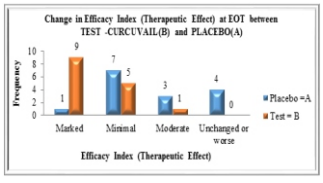
Table 18 (B): Change in Severity of Therapeutic Effect from Baseline to the EOT (Placebo = A)

Change in Efficacy Index (Therapeutic Effect) from Baseline to the EOT (Placebo = A)		
Outcome	Baseline	EOT
Marked	1	1
Minimal	3	7
Moderate	3	3
Unchanged or worse	8	4

Table 18 ©: Change in Severity of Therapeutic Effect at EOT between TEST -CURCUVAIL (B) and PLACEBO (A)

Change in Efficacy Index (Therapeutic Effect) at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)			
Outcome	Placebo =A	TEST -CURCUVAIL = B	P-Value
Marked	1	9	0.0084
Minimal	7	5	
Moderate	3	1	
Unchanged or worse	4	0	
Total	15	15	

Fig. 11 – Change in Therapeutic Effect at EOT between TEST - CURCUVAIL(B) and PLACEBO(A)



VII. X-ray &Anti-CCP (anti-cyclic citrullinated peptide) TEST - CURCUVAIL result analysis

1. Change in X-Ray of Knee joint PA view

Change in X-Ray of Knee joint PA view for TEST -CURCUVAIL – B & Placebo - A arms were assessed from lab report. As per Table 19(A), it is evident that, all 15 patient X-ray report was abnormal NCS at Baseline but at the End of Treatment all patient X-ray report were normal in TEST -CURCUVAIL (B) arm, whereas all 15patientX-ray report was clinically abnormal NCS at Baseline but at the End of Treatment only 1 patients X-ray report were normal and 14 patient X-ray report was abnormal in Placebo (A) arm (Table 19B & Fig. 12).

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

Considering Table 19(A), 19 (B) &19 (C) we can observe that improvement in X-ray report of Knee joint analysis was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm,

respectively and the same has been reflected in Fig. 64.So this proves the efficacy of TEST -CURCUVAIL (B) over Placebo (A).

Table 19(A): Change in X-Ray of Knee joint PA view score of from Baseline to the EOT (TEST -CURCUVAIL = B)

Change in X-Ray of Knee joint PA view from Baseline to the EOT (TEST -CURCUVAIL = B)		
Outcome	Baseline	EOT
Abnormal NCS	15	0
Normal	0	15

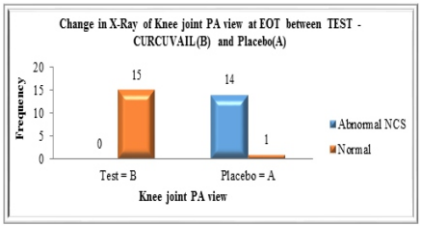
Table 19(B):Change in X-Ray of Knee joint PA view score of from Baseline to the EOT (Placebo = A)

Change in X-Ray of Knee joint PA view from Baseline to the EOT (Placebo = A)		
Outcome	Baseline	EOT
Abnormal NCS	15	14
Normal	0	1

Table 19(C):Change in X-Ray of Knee joint PA view score of at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)

Change in X-Ray of Knee joint PA view at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)			
Outcome	Abnormal NCS	Normal	P- value
TEST -CURCUVAIL = B	0	15	<.0001
Placebo = A	14	1	

Fig. 12 –Change in X-Ray of Knee joint PA view score of at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)



2. Change in X-ray of hand

Change in X-Ray of hand for TEST -CURCUVAIL – B & Placebo - A arms were assessed from lab report. As per Table 20(A),it is evident that, all 15 patient X-ray report was abnormal NCS at Baseline but at the End of Treatment only 3 patient X-ray report was clinically abnormal NCS and 12 patient normal in TEST -CURCUVAIL (B) arm, whereas all 15patient X-ray report was abnormal NCS at Baseline but at the End of Treatment only 2patientX-ray report were normal and 13patient X-ray report was clinically abnormal in Placebo (A) arm(Table 20(B) & Fig. 13).

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

Considering Table 20(A), 20(B) &20(C) we can observe that improvement in X-ray report of hand analysis was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 13.So this proves the efficacy of TEST -CURCUVAIL (B) over Placebo (A).

Table 20(A): Change in X-Ray of X-ray of hand score of from Baseline to the EOT (TEST -CURCUVAIL = B

Change in X-ray of hand from Baseline to the EOT (TEST -CURCUVAIL = B)		
Outcome	Baseline	EOT
Abnormal NCS	15	3
Normal	0	12

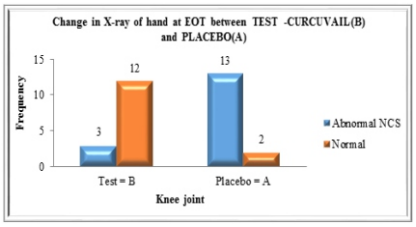
Table 20(B): Change in X-Ray of X-ray of hand score of from Baseline to the EOT (Placebo = A)Change in X-ray of hand from Baseline to the EOT (Placebo = A)

Change in X-ray of hand from Baseline to the EOT (Placebo = A)		
Outcome	Baseline	EOT
Abnormal NCS	15	13
Normal	0	2

Table 20©: Change in X-Ray of X-ray of hand score of at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)

Change in X-Ray of Knee joint PA view at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)			
Outcome	Abnormal NCS	Normal	P- value
TEST -CURCUVAIL = B	3	12	<.0001
Placebo = A	13	2	

Fig. 13 –Change in X-Ray of X-ray of hand score of at EOT between TEST -CURCUVAIL (B) and PLACEBO (A)



IX. Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL

Change in Anti-CCP TEST -CURCUVAIL analysis for TEST -CURCUVAIL – B & Placebo - A arms were assessed from lab report. As per Table 21(A),it is evident that all 15 patient Anti-CCP TEST -CURCUVAIL report was clinically abnormal NCS at Baseline but at the End of Treatment only 2patientAnti-CCP TEST -CURCUVAIL report abnormal NCS and 13patient normal in TEST -CURCUVAIL (B) arm, whereas all 15patientAnti-CCP TEST -CURCUVAIL report was clinically abnormal NCS at Baseline but at the End of Treatment only 1patientAnti-CCP TEST -CURCUVAIL report were normal and 14patientAnti-CCP TEST -CURCUVAIL report was abnormal in Placebo (A) arm (Table 21(B) & Fig. 14).

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

Considering Table 21(A), 21(B) &21(C) we can observe that improvement in Anti-CCP TEST -CURCUVAIL report was more for TEST -CURCUVAIL-B arm in comparison to the Placebo-A arm, respectively and the same has been reflected in Fig. 66.So this proves the efficacy of TEST -CURCUVAIL (B) over Placebo (A).

Table 21(A): Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL score of from Baseline to the EOT (TEST -CURCUVAIL = B)

Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL from Baseline to the EOT TEST -CURCUVAIL = B)		
Outcome	Baseline	EOT
Abnormal NCS	15	2
Normal	0	13

Table 21(B): Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL score of from Baseline to the EOT (Placebo = A)

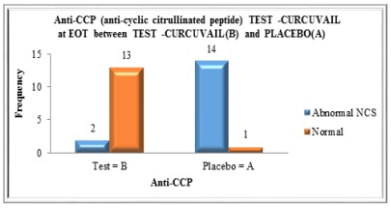
Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL from Baseline to the EOT (Placebo = A)		
Outcome	Baseline	EOT

Abnormal NCS	15	14
Normal	0	1

Table 21©: Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL score of at EOT between TEST -CURCUVAIL (B) and PLACEBO

Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)			
Outcome	Abnormal NCS	Normal	P- value
TEST -CURCUVAIL = B	2	13	<.0001
Placebo = A	14	1	

Fig. 14 –Change in Anti-CCP (anti-cyclic citrullinated peptide) TEST -CURCUVAIL score of at EOT between TEST -CURCUVAIL (B) and PLACEBO (A)



Secondary Endpoints: -

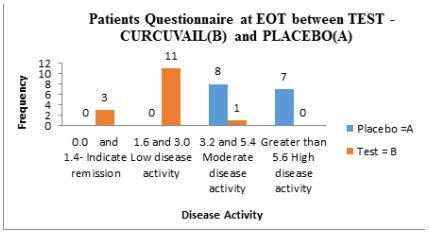
Secondary parameters considered in the study for comparing the efficacy between TEST -CURCUVAIL (B) and Placebo (A) were PatientQuestionnaire to ask to understand the improvement in Rheumatoid Arthritis disease activity.

Frequency distribution was used to compile the scores with their interpretations for Questionnaire to ask to understand the improvement in Rheumatoid Arthritis disease activity by patients' self-assessments.

Table 22(A)		
Patients Questionnaire from Baseline to the EOT (TEST -CURCUVAIL = B)		
	BASELINE	EOT
0.0 and 1.4- Indicate remission	0	3
1.6 and 3.0 Low disease activity	0	11
3.2 and 5.4 Moderate disease activity	0	1
Greater than 5.6 High disease activity	15	0

Table 22(B)		
Patients Questionnaire from Baseline to the EOT (PLACEBO = A)		
	BASELINE	EOT
0.0 and 1.4- Indicate remission	0	0
1.6 and 3.0 Low disease activity	0	0
3.2 and 5.4 Moderate disease activity	0	8
Greater than 5.6 High disease activity	15	7

Table 22(C)				
Patients Questionnaire at EOT between TEST -CURCUVAIL(B) and PLACEBO(A)				
Outcome	0.0 and 1.4- Indicate remission	1.6 and 3.0 Low disease activity	3.2 and 5.4 Moderate disease activity	Greater than 5.6 High disease activity
Placebo =A	0	0	8	7
TEST -CURCUVAIL = B	3	11	1	0



All 15 patients' disease activity were Greater than 5.6 at baseline visit and at the EOT out of 15 patient, 11 patient were having low disease activity in range of 1.6 and 3.0, 3 patient indicate remission in range of 0.0 and 1.4 and 1 patients were having moderate disease activity in range of 3.2 and 5.4 TEST -CURCUVAIL (B) arm.

Whereas, All 15 patients' disease activity were Greater than 5.6 at baseline visit and at the EOT out of 15 patient 8 patient were having Moderate disease activity in range of 3.2 and 5.4 and 7 patient were having disease activity Greater than 5.6 in placebo (A) arm.

It is evident from the above discussion that CURCUMIN is effective in alleviating the symptoms of joint swelling and tenderness, pain, duration of morning stiffness and also improving the quality of life in Rheumatoid Arthritis patients.

No Adverse events/Serious Adverse events were reported during the entire phase of clinical trial and hence concluded that Investigational product is safe to use and well tolerated in Study patient.

DISCUSSION AND CONCLUSION:-

Rheumatoid Arthritis is a form of joint disorder characterized by chronic inflammation in one or more joints that usually results in pain and is often disabling. Rheumatoid Arthritis includes more than 100 different forms: like rheumatoid Arthritis, psoriatic Rheumatoid Arthritis, and related autoimmune diseases.

The major goal of Rheumatoid Arthritis treatment is to reduce joint pain induced by inflammation in the joints, daily wear and tear of joints, and muscle strains.

Herbal therapies with anti-inflammatory properties and minimum side effects are needed for the treatment of Rheumatoid Arthritis, including rheumatoid Arthritis and osteoarthritis. The purpose of this study was to systemically evaluate randomized clinical trials (RCTs) of Curcumin for treating Rheumatoid Arthritis symptoms.

This study was done on 30 patients with symptoms of Rheumatoid arthritis. Patients were selected as per the inclusion criteria. It was a double blinded study where patients were allocated into 2 arms PLACEBO and TEST -CURCUVAIL arm as per the randomization chart generated.

Efficacy analysis was performed on all 30 patients who completed the trial. The results obtained from Intra-Group statistical analyses and Efficacy analyses of primary endpoints between the TEST -CURCUVAIL and PLACEBO showed statistically significant improvement in symptoms of rheumatoid arthritis in TEST -CURCUVAIL (CURCUMIN) arm.

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

The study concludes that, TEST -CURCUVAIL (CURCUMIN) due to its anti-inflammatory and immunomodulatory effect it is more efficacious and safer in comparison to PLACEBO (B) in treatment of chronic joint pain due to rheumatoid arthritis

The study concluded that CURCUMIN is safe and effective and is clinically proven for treatment of chronic joint pain in patients with

Rheumatoid Arthritis.

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