

## A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP CLINICAL STUDY TO EVALUATE THE ANALGESIC EFFECT OF AQUEOUS EXTRACT OF *TERMINALIA CHEBULA*, A PROPRIETARY CHROMIUM COMPLEX, AND THEIR COMBINATION IN SUBJECTS WITH JOINT DISCOMFORT

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### ABSTRACT

**Objective:** To evaluate the analgesic effect of an aqueous extract of *Terminalia chebula* (TCE), a proprietary chromium complex (PCC), and their combination in subjects with joint discomfort.

**Methods:** A total of 100 patients with knee joint discomfort were randomized into five treatment groups - TCE 500 mg BID, TCE 500 mg BID+PCC 400 µg OD, PCC 400 µg OD alone, placebo, and TCE 250 mg BID, for 12 weeks in a double-blinded manner. Assessment of symptoms of knee joint pain and discomfort was done by modified Western Ontario and McMaster Universities Arthritis Index (mWOMAC) and knee swelling index (KSI); visual analog scale (VAS) was used for subjective assessment of pain, stiffness, and disability. Statistical analysis was done with GraphPad Prism 6.

**Results:** Absolute reduction in mWOMAC score in TCE 500 mg (19.82±8.35), TCE 500 mg+PCC 400 µg (13.10±5.69), PCC 400 µg (8.30±3.81), placebo (2.45±3.07), and TCE 250 mg (10.47±4.43), respectively, at the end of 12 weeks as compared to the baseline values. Absolute reduction in KSI in TCE 500 mg (28.95±16.82), TCE 500 mg+PCC 400 µg (19.14±9.50), PCC 400 µg (12.7±4.86), placebo (10.03±3.8), and TCE 250 mg (18.24±6.86), respectively, at the end of 12 weeks as compared to the baseline values ( $p < 0.001$ ). Similar results were seen with VAS assessments for pain, stiffness, and disability. All the treatments were well tolerated.

**Conclusion:** TCE and PCC reduce joint discomfort.

**Keywords:** *Terminalia chebula* extract, Proprietary chromium complex, Western Ontario and McMaster Universities Arthritis Index.

### INTRODUCTION

Joint discomfort may be an early indication of the onset of osteoarthritis (OA). OA is a non-inflammatory, degenerative disorder of joints characterized by progressive deterioration of the articular cartilage and formation of new bone (osteophytes) [1]. It is estimated to be the fourth leading cause of disability worldwide (10% males and 13% females). In Asia, prevalence rates of OA of the knee were found to be high in elderly people, especially women [2]. In India, the prevalence of OA of the knee ranges from 22% to 39% [3]. During a 1-year period, 25% of people over 55 years may demonstrate persistent episode of knee pain. In the same period, about one in six has to consult their general practitioner about knee pain. About 10% of people aged over 55 years have painful, disabling OA of the knee, of whom one-quarter are severely disabled [4].

While non-steroidal anti-inflammatory drugs (NSAIDs) are effective for the treatment of pain and are overall well tolerated, their use is associated with potentially severe adverse effects. Gastrointestinal (GI) complications from NSAIDs include dyspepsia, ulcers, and bleeding [5,6]. Epidemiologic studies suggest that use of NSAIDs increases the risk of GI complications 2-6 times [7]. A safer alternative treatment would, therefore, be beneficial in such cases. Natural products derived from plants offer such an alternative.

*Terminalia chebula* (TC) is a plant commonly used in ayurvedic medicine for the treatment of arthritis, gout, and paralysis. Both anecdotal evidence and recent studies have implicated the potential of this herbal remedy for the treatment of painful, chronic arthritic type conditions in experimental models [8,9]. Animal studies have demonstrated the

anti-inflammatory activity of the ethanolic extract of TC fruits, and the probable mechanism of action was postulated to be due to inhibition of cyclooxygenase 1 and 2, and 5-lipoxygenase enzymes [10]. Another mechanism, which can be attributed to TC's anti-inflammatory action, could be downregulation of nuclear factor kappa-light-chain-enhancer of activated B-cells [11]. Another study has demonstrated the anti-inflammatory properties of a polyherbal formulation for allergic rhinitis, containing TC as one of the several ingredients [12].

Proprietary chromium complex (PCC) is a complex of chromium III with the polyphenolic compounds of *Phyllanthus emblica* fruit extract and purified Shilajit, a natural product from the Himalayas, containing dibenzo- $\alpha$ -pyrones (DBPs), DBP-chromoproteins, and fulvic acids. A recent study has shown that this complex decreased pain associated with OA in dogs [13].

No human clinical studies of TC or PCC in subjects with joint pain and discomfort have been reported so far. Thus, the present clinical study was aimed at evaluating the efficacy and safety of an aqueous extract of TC (TCE) at two different doses, PCC alone and a combination of both in human volunteers with joint discomfort.

### METHODS

The aqueous TCE used in this study was AyuFlex® (Natreen Inc., New Jersey, USA), which is a water-soluble product derived from the edible fruits of TC, an ancient ayurvedic plant, and standardized for its bioactive compounds, chebulinic acid plus chebulagic acid not <27% and other low molecular weight hydrolysable tannins not <12% along with gallic

acid and ellagic acid. The high-performance liquid chromatography of the aqueous TCE used in this study is shown in Fig. 1.

PCC was supplied by Natrean, Inc., under the brand name, Crominex<sup>®</sup>, which is a capsule. The excipients used in the capsule formulation include microcrystalline cellulose, silicon dioxide, talc, gelatin (from the capsule shell), and magnesium stearate.

This study was a prospective, randomized, double-blind and placebo-controlled trial conducted in the Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, India, after approval from Institutional Ethics Committee and, after all, the subjects had given written informed consent before their participation in the study. The Clinical Trials Registry - India number is REF/2015/12/010342. A total of 110 patients were screened, and 100 patients were enrolled to receive the study treatment in a randomized manner.

#### Inclusion criteria

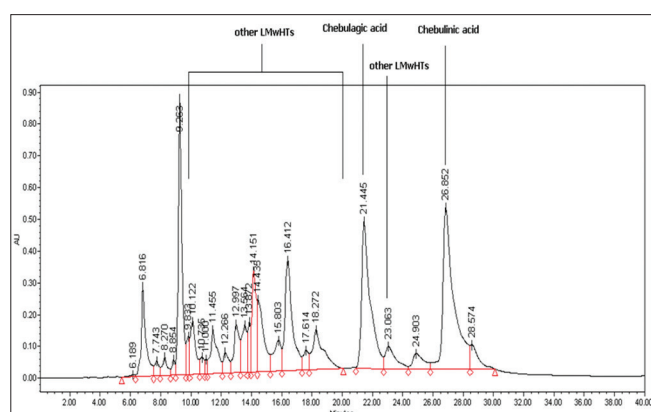
Subjects of either gender aged between 40 and 70 years, suffering from joint discomfort for at least 6 months duration, taking only an over the counter analgesic medication occasionally and meeting the American Rheumatism Association (ARA) functional Class I to III and radiological evidence of OA (patients who had Grade II to IV of the Kellgren and Lawrence scale [14] in the knee joint X-ray) and who recorded baseline pain scores of at least 40 mm on the visual analog scale (VAS), monitored at baseline visit, and who agreed to discontinue any use of analgesics during the study were enrolled.

#### Exclusion criteria

Patients with severe OA (ARA functional Class IV), radiological grading - Kellgren and Lawrence scale ranging from Grade 0 to Grade I, on alternative system of medicine, any psychiatric disorder or who have been using systemic/intra-articular steroids within 12 weeks and hyaluronic acid in the last 9 months, or potential candidates for imminent joint replacement, patients with uncontrolled hypertension or diabetes, hepatic or renal impairment, pregnant or lactating females, or with a recent trauma of the involved knee were excluded from the study.

#### Procedure

After screening, all the eligible subjects were randomized to either of the following five treatment groups in a double-blinded and double-dummy fashion for a duration of 12 weeks: Group (A) - 1 capsule of TCE 500 mg twice a day and an identical placebo of PCC once daily after food; Group (B) - 1 capsule of TCE 500 mg twice a day and 1 capsule of 400 µg of PCC once a day after food; Group (C) - 1 capsule of 400 µg of PCC once a day and an identical placebo of TCE twice daily after food; Group (D) - identical placebo capsules two in the morning and one in the evening after food; Group (E) - 1 capsule of TCE 250 mg twice a day and an identical placebo of PCC once daily after food.



**Fig. 1: High-performance liquid chromatography chromatogram of aqueous extract of *Terminalia chebula***

Subjects were scheduled for follow-up visits at 4, 8, and 12 weeks of therapy and were assessed using modified Western Ontario and McMaster Universities Arthritis Index (mWOMAC) [15], knee swelling index (KSI), and VAS for pain, stiffness, and disability, all of which were recorded at baseline, 4, 8, and 12 weeks (end of treatment). The patients were allowed to take paracetamol (acetaminophen) 650 mg tablets as rescue medication, and the total count of rescue medication used was recorded at the end of the study. Safety lab investigations for hematological, hepatic, and renal biochemical parameters were conducted before the beginning and at the end of the study and also as if and when required. At each visit, they were evaluated for efficacy and safety. Subjects were enquired for the presence of adverse drug reaction, and the same was recorded in the case report form. Compliance to therapy was assessed by pill count method.

#### Primary outcome measure

The mWOMAC index is a disease-specific outcome measure for OA. It has three subscales assessing: Pain - A (5 questions), stiffness - B (2 questions), and physical function for disability - C (17 questions). This outcome was measured at baseline, 4, 8, and 12 weeks. In this study, the primary outcome was the reduction in the mWOMAC total score (A + B + C) from baseline to the end of treatment at week 12.

#### Secondary outcome measures

It was assessed by VAS based assessment of pain, disability, and stiffness subscales, wherein pain subscale assessed by: No pain (0 mm) to extreme pain (100 mm); stiffness subscale assessed by: No stiffness (0 mm) to extreme stiffness (100 mm); disability subscale assessed by: No disability (0 mm) to extreme disability (100 mm); KSI as measured by signal joint knee circumference; use of rescue medication in all treatment groups; physician global assessment - Characterized by five categories: Excellent - complete relief of symptoms; good - partial relief of symptoms; fair - minimal relief of symptoms; poor - no relief of symptoms; very poor - worsening of symptoms.

#### Statistical analysis

With a confidence level of 95%, power of 80%,  $p < 0.05$ , and a dropout rate of 10% a total sample size of 110 was taken for the study. Data are expressed as mean  $\pm$  standard deviation. Primary and secondary outcome measures were analyzed as the absolute change and mean percentage reduction in the response over 4, 8, and 12-week treatment period. Paired t-test was used to compare the mean change from baseline to post-treatment within group and ANOVA for between group comparisons. All statistical analyses were performed using the GraphPad Prism software 6.0 (GraphPad Software Inc., San Diego, California, USA).

#### RESULTS

A total of 110 OA patients were screened, and 100 subjects completed the study. A total of 22 subjects in TCE 500 mg group, 21 subjects in TCE 500 mg and the PCC combination group, 17 subjects in TCE 250 mg group, and 20 subjects each in the PCC and placebo groups completed the study. The detailed demographic characteristics of all the five study groups are shown in Table 1. There were no significant differences between treatment groups in baseline characteristics including age, weight, and body mass index, indicating a homogenous population.

The results of efficacy parameters at the end of 4 weeks are shown in Table 2. At the end of 4 weeks of the study, the baseline values of all the parameters were comparable in all the treatment groups except placebo. There was a significant reduction of all parameters (scores) after 4 weeks of treatment compared to baseline in all the treatment groups except placebo ( $p < 0.001$ ).

At the end of 8 weeks of the study, the baseline values of all the efficacy parameters were comparable in all the treatment groups except placebo as shown in Table 3. There was a significant reduction of all

Table 1: Demographic data

Variables	TCE 500 mg (A)	TCE 500 mg+PCC (B)	PCC (C)	Placebo (D)	TCE 250 mg (E)
Total (N)	22	21	20	20	17
Gender (M/F)	9/13	10/11	13/7	12/8	9/8
Age (years)	59.18±8.20	57.67±8.11	55.9±9.06	58.05±6.07	58.35±8.36
Weight (kg)	75.51±5.37	68.43±14.88	61.63±6.43	75.9±8.24	75.41±11.08
BMI (kg/m <sup>2</sup> )	29.54±6.94	26.67±5.29	26.14±2.03	28.5±3.73	27.47±2.98

BMI: Body mass index, TCE: *Terminalia chebula* extract, PCC: Proprietary chromium complex

Table 2: Results at 4 weeks

Outcome measures	Baseline	End of 4 weeks	Absolute change	Mean percentage change
<b>mWOMAC scores</b>				
TCE 500 mg (A)	53.45±7.42	43.73±7.40*	9.73±4.46* <sup>ⓐ</sup>	18.22±7.73* <sup>ⓐ</sup>
TCE 500 mg+PCC (B)	53.00±5.96	46.14±4.45*	6.86±3.60*	12.62±6.05*
PCC (C)	54.00±5.47	51.75±6.37*	2.25±1.80*	4.32±3.61*
Placebo (D)	51.95±6.53	51.45±6.55	0.5±0.83	0.97±1.62
TCE 250 mg (E)	51.18±7.45	44.12±6.96*	7.06±4.07	13.55±7.41
<b>KSI</b>				
TCE 500 mg (A)	401.09±43.93	385.55±36.03*	15.55±15.35**	3.66±3.50
TCE 500 mg+PCC (B)	366.19±29.57	355.76±31.89*	10.43±7.05*	2.90±2.10
PCC (C)	360.9±20.87	354.90±20.12*	6±3.58	1.65±0.99
Placebo (D)	404.1±25.79	404.95±25.00	-0.85±1.69	-0.22±0.45
TCE 250 mg (E)	399.71±37.26	390.00±36.83*	9.71±3.80	2.43±0.95
<b>Pain</b>				
TCE 500 mg (A)	69.36±5.69	54.09±8.40*	15.27±7.23**	22.02±9.92*
TCE 500 mg+PCC (B)	72±4.30	62.48±5.59*	9.52±4.45**	13.21±6.15**
PCC (C)	71±4.47	67.25±4.72*	3.75±2.75 <sup>ⓐ</sup>	5.25±3.80 <sup>ⓐ</sup>
Placebo (D)	66.4±6.95	66.75±6.67	-0.30±1.57	-0.60±2.70
TCE 250 mg (E)	69.76±6.74	61.53±6.22*	8.24±5.12	11.59±6.62
<b>Stiffness</b>				
TCE 500 mg (A)	63.59±8.51	48.64±10.26*	14.95±6.67**	23.70±10.41*
TCE 500 mg+PCC (B)	67.24±2.95	59.52±4.15*	7.71±3.70**	11.43±5.45*
PCC (C)	62.5±3.69	60.75±4.00 <sup>#</sup>	1.75±3.04*	2.74±4.67*
Placebo (D)	65±3.97	65.25±4.72	-0.25±1.97	-0.36±3.14
TCE 250 mg (E)	62.41±6.03	53.12±6.58*	9.29±4.33*	14.88±6.43
<b>Disability</b>				
TCE 500 mg (A)	57.95±8.72	45.59±11.50*	12.36±7.83*	21.55±13.54*
TCE 500 mg+PCC (B)	65.76±5.31	57.62±4.07*	8.14±4.29*	12.13±5.72*
PCC (C)	61.50±4.39	60.90±4.30 <sup>ⓐ</sup>	0.6±1.19 <sup>#</sup>	0.95±1.86*
Placebo (D)	61.5±2.35	63.25±3.73	-1.75±2.94	-2.85±4.71
TCE 250 mg (E)	56.59±3.59	50.59±4.64*	6.00±4.62	10.45±8.29

<sup>ⓐ</sup>p<0.05, \*p<0.01, \*\*p<0.001 compared to baseline. Absolute change: WOMAC score - \*A versus C, A versus D, B versus D, D versus E, B versus C, C versus E (p<0.001), <sup>ⓐ</sup>A versus B (p<0.05), KSI - \*A versus D, B versus D (p<0.001), <sup>#</sup>A versus C, D versus E (p<0.01), Pain - \*A versus C, A versus D, A versus E, B versus D, D versus E (p<0.001), <sup>#</sup>A versus B, B versus C (p<0.01), <sup>ⓐ</sup>C versus E (p<0.05), Stiffness - \*A versus B, A versus C, A versus D, A versus E, B versus C, B versus D, C versus E, D versus E (p<0.001), <sup>#</sup>A versus E, B versus C (p<0.01), Disability - \*A versus C, A versus D, A versus E, B versus C, B versus D, D versus E (p<0.001), <sup>#</sup>C versus E (p<0.01), <sup>ⓐ</sup>A versus B (p<0.05), Mean percentage change: WOMAC score - \*A versus C, A versus D, B versus C, B versus D, C versus E, D versus E (p<0.001), <sup>ⓐ</sup>A versus B (p<0.05), KSI - \*A versus D, B versus D (p<0.001), <sup>#</sup>D versus E (p<0.01), <sup>ⓐ</sup>A versus C, C versus D (p<0.05), Pain - \*A versus B, A versus D, A versus E, B versus D, D versus E (p<0.001), <sup>#</sup>B versus C (p<0.01), <sup>ⓐ</sup>C versus D, C versus E (p<0.05), Stiffness - \*A versus B, A versus C, A versus D, A versus E, B versus C, B versus D, C versus E, D versus E (p<0.001), Disability - \*A versus B, A versus C, A versus D, A versus E, B versus C, B versus D, C versus E, D versus E (p<0.001). TCE: *Terminalia chebula* extract, PCC: Proprietary chromium complex, WOMAC: Western Ontario and McMaster Universities Arthritis Index, KSI: Knee swelling index

parameters (scores) after 8 weeks of treatment compared to baseline in all the treatment groups except placebo (p<0.001).

At the end of 12 weeks, the baseline values of the mWOMAC score, KSI, VAS for pain, stiffness, and disability were comparable in all the five treatment groups as seen in Table 4. There was a significant reduction in all the above-mentioned parameters after 12 weeks of treatment compared to baseline in all the five treatment groups (p<0.001).

The number of rescue medications that were used by the subjects in all the five groups during the study was noted. It was found that the usage of paracetamol 650 mg tablets were the least in TCE 500 mg group and the highest in the placebo group. All safety hematological, hepatic, and renal biochemical parameters were within normal limits with all the four treatment groups. Two subjects in TCE 500 mg group complained of dyspepsia, and one had diarrhea. In the PCC 400 µg group, two subjects had diarrhea while two subjects in the combination group had dyspepsia and vomiting. None of the patients in either group had

any serious side effects, and no subjects discontinued the study due to adverse events.

## DISCUSSION

The outcome parameters used to assess the efficacy of treatment groups were mWOMAC score, KSI, and VAS for pain, stiffness, and disability. The baseline values of all efficacy outcome parameters were comparable in all 5 treatment groups with significant reductions being seen in all these groups after 4, 8, and 12 weeks of treatment compared to baseline (p<0.001). As the primary outcome was, changes in various parameters from baseline to the end of treatment at week 12, the same has been discussed in the following lines.

In this study, treatment with TCE 500 mg twice daily (A) for 12 weeks resulted in significant reductions in mWOMAC score when compared with all other treatment groups - TCE 500 mg and PCC combination (B) p<0.01, PCC alone (C) (p<0.001), Placebo (D) (p<0.001) as well

Table 3: Results at 8 weeks

Outcome measures	Baseline	End of 8 weeks	Absolute change	Mean percentage change
<b>mWOMAC scores</b>				
TCE 500 mg (A)	53.45±7.42	37.59±6.66*	15.86±7.22*	29.11±10.96*
TCE 500 mg+PCC (B)	53.00±5.96	43.33±5.21*	9.67±3.71*	18.05±6.25*
PCC (C)	54.00±5.47	50.60±5.85*	3.40±1.85 <sup>®</sup>	6.37±3.45 <sup>#</sup>
Placebo (D)	51.95±6.53	50.8±6.09	1.15±1.42	2.11±2.55
TCE 250 mg (E)	51.18±7.45	43.18±7.54*	8±4.91	15.42±9.33
<b>KSI</b>				
TCE 500 mg (A)	401.09±43.93	383.27±36.87*	17.82±15.73**	4.25±3.60* <sup>®</sup>
TCE 500 mg+PCC (B)	366.19±29.57	352.00±32.18*	14.19±9.26*	3.92±2.73*
PCC (C)	360.9±20.87	352.7±18.97*	8.2±4.47 <sup>®</sup>	2.24±1.19 <sup>®</sup>
Placebo (D)	404.1±25.79	403.95±25.82	0.15±0.67	0.04±0.17
TCE 250 mg (E)	399.71±37.26	387.23±36.44*	12.35±6.32	3.09±1.58
<b>Pain</b>				
TCE 500 mg (A)	69.36±5.69	49.32±9.92*	20.05±8.63**	28.99±11.94**
TCE 500 mg+PCC (B)	72±4.30	57.14±5.14*	14.86±5.28 <sup>#</sup>	20.53±6.84 <sup>#</sup>
PCC (C)	71±4.47	60.50±7.24*	10.50±6.26	14.78±8.65
Placebo (D)	66.4±6.95	59.70±7.43	6.70±8.58	9.38±13.38
TCE 250 mg (E)	69.76±6.74	57.76±7.25*	12.00±6.54	17.01±8.56
<b>Stiffness</b>				
TCE 500 mg (A)	63.59±8.51	45.00±10.91*	18.59±7.04*	29.53±11.10*
TCE 500 mg+PCC (B)	67.24±2.95	56.67±4.28*	10.57±4.17	15.67±5.98
PCC (C)	62.5±3.69	54.85±4.60*	7.65±4.60	12.12±7.06
Placebo (D)	65±3.97	57.50±6.59	7.5±5.50	11.53±8.62
TCE 250 mg (E)	62.41±6.03	51.76±5.83*	10.65±3.81	17.00±5.65
<b>Disability</b>				
TCE 500 mg (A)	57.95±8.72	44.32±9.55*	13.64±5.74*	23.53±9.56*
TCE 500 mg+PCC (B)	65.76±5.31	54.76±4.32*	11.00±4.90* <sup>®</sup>	16.46±6.67*
PCC (C)	61.50±4.39	54.80±5.13*	6.7±5.89*	10.59±9.35*
Placebo (D)	61.5±2.35	61.50±2.35	Nil	Nil
TCE 250 mg (E)	56.59±3.59	49.59±4.85*	7.00±4.20	12.31±7.51

<sup>®</sup>p<0.05, <sup>#</sup>p<0.01, <sup>\*</sup>p<0.001 compared to baseline. Absolute change: WOMAC score - \*A versus B, A versus C, A versus D, A versus E, B versus C, B versus D, D versus E (p<0.001), <sup>®</sup>C versus E (p<0.05), KSI - \*A versus D, B versus D, D versus E (p<0.001), <sup>#</sup>A versus C (p<0.01), <sup>®</sup>C versus D (p<0.05), Pain - \*A versus C, A versus D (p<0.001), <sup>#</sup>A versus E, B versus D (p<0.01), Stiffness - \*A versus B, A versus C, A versus D, A versus E (p<0.001), Disability: \*A versus C, A versus D, A versus E, B versus D, C versus D, D versus E (p<0.001), <sup>®</sup>B versus C (p<0.05), Mean percentage change: WOMAC score - \*A versus B, A versus C, A versus D, A versus E, B versus C, B versus D, D versus E (p<0.001), <sup>#</sup>C versus E (p<0.01), KSI - \*A versus D, B versus D, D versus E (p<0.001), <sup>®</sup>A versus C, C versus D (p<0.05), Pain - \*A versus C, A versus D (p<0.001), <sup>#</sup>A versus E, B versus D (p<0.01), Stiffness - \*A versus B, A versus C, A versus D, A versus E (p<0.001), Disability - \*A versus C, A versus D, A versus E, B versus D, C versus D, D versus E (p<0.001). TCE: *Terminalia chebula* extract, PCC: Proprietary chromium complex, mWOMAC: Modified Western Ontario and McMaster Universities Arthritis Index, KSI: Knee swelling index

as TCE 250 mg twice daily (E) (p<0.001). However, the combination of TCE 500 mg and PCC (B) resulted in significant reductions in mWOMAC scores when compared with PCC alone (p<0.01) and placebo (p<0.001) only. Similarly, TCE 250 mg twice daily reduced mWOMAC scores significantly when compared with PCC and placebo (p<0.001) only. TC contains high levels of hydrolysable tannins such as chebulagic acid, chebulinic acid, and gallic acid that have antiarthritic effects [16]. Gallic acid has been identified as a pharmacologically active compound with antioxidative, antimutagenic, anticarcinogenic, anti-inflammatory, and hepatoprotective activities. Gallic acid and chebulagic acid inhibit T-cell-mediated cytotoxicity. Chebulagic acid also has been shown to suppress the expression of tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6) [17-19]. Both these properties may be contributing to its anti-inflammatory effect in animals. Furthermore, TCE extracts have been shown to scavenge nitrous oxide free radicals *in vitro*, which may also explain their anti-inflammatory activity [20,21]. This indicates that TCE 500 mg twice daily (A) has significant anti-inflammatory effect in the affected joints. Similarly, this anti-inflammatory effect was also seen in the reduction of KSI scores in this study. Treatment with TCE 500 mg twice daily (A) for 12 weeks resulted in significant reduction in the KSI when compared with other treatment groups (p<0.01). The combination of TCE 500 mg and PCC (B) showed significant reduction when compared with PCC alone (C) (p<0.01) and placebo (D) (p<0.01). TC 250 mg twice daily (E) showed significant reduction when compared to placebo (D) (p<0.001) only. PCC (C) alone produced significant reduction when compared with placebo (D) (p<0.05) and TCE 250 mg twice daily (E) (p<0.01).

Subjects in the treatment group of TCE 500 mg showed significant reductions in the absolute and mean percent reductions in the scores of VAS for pain, stiffness, and disability when compared to other treatment groups (p<0.001). The combination of TCE 500 mg and PCC (B) produced significant reductions in the absolute change when compared with PCC (C) in VAS pain (p<0.05) and disability (p<0.01). TCE 250 mg (E) produced significant absolute change reductions in VAS stiffness and disability when compared to placebo (D) (p<0.05). For VAS disability, the combination of TCE 500 mg and PCC (B) showed significant mean percentage reduction when compared with PCC alone (C) (p<0.01). TC has also been shown to have chondroprotective activity by acting as a highly potent inhibitor of hyaluronidase and collagenase activity [22]. This chondroprotective activity was demonstrated in this study by the subjective assessment of patients using the VAS scales for pain, stiffness, and disability.

Cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-17 induce joint destruction by activating osteoclasts through increased RANKL expression on synovial fibroblast and by stimulating chondrocytes to produce matrix metalloproteinases [23]. TCE has been shown to reduce serum TNF- $\alpha$  level and synovial expression of TNF-R1, IL-6, and IL-1  $\beta$  [24]; and this may be the reason for its anti-inflammatory property.

The number of rescue medications used by the subjects was the least in the TCE 500 mg twice daily group (A) (mean of 7±1.11), supporting the analgesic efficacy of TCE. All the treatment groups were tolerated without any serious adverse events.



Table 4: Results at 12 weeks

Outcome measures	Baseline	End of 12 weeks	Absolute change	Mean percentage change
<b>mWOMAC scores</b>				
TCE 500 mg (A)	53.45±7.42	33.64±7.54*	19.82±8.35**	36.53±14.50**#
TCE 500 mg+PCC (B)	53.00±5.96	39.90±9.86*	13.10±5.69**NS	25.18±11.32**NS
PCC (C)	54.00±5.47	45.70±4.33*	8.30±3.81**NS	15.09±6.17 <sup>NS</sup>
Placebo (D)	51.95±6.53	49.5±6.13 <sup>NS</sup>	2.45±3.07 <sup>NS</sup>	4.52±6.25
TCE 250 mg (E)	51.18±7.45	40.71±6.14*	10.47±4.43* <sup>NS</sup>	20.11±7.71*
<b>KSI</b>				
TCE 500 mg (A)	401.09±43.93	372.14±39.66*	28.95±16.82* <sup>#</sup>	7.10±3.81* <sup>#</sup>
TCE 500 mg+PCC (B)	366.19±29.57	347.05±32.59*	19.14±9.50* <sup>#</sup> <sup>NS</sup>	5.29±2.84* <sup>NS</sup>
PCC (C)	360.9±20.87	348.2±18.45*	12.7±4.86* <sup>#</sup>	3.48±1.27 <sup>#</sup>
Placebo (D)	404.1±25.79	393.8±25.45 <sup>#</sup>	10.38±3.8 <sup>#</sup>	2.55±0.93 <sup>NS</sup>
TCE 250 mg (E)	399.71±37.26	381.47±36.63*	18.24±6.86* <sup>NS</sup>	4.56±1.73*
<b>Pain</b>				
TCE 500 mg (A)	69.36±5.69	44.95±10.71*	24.41±9.59*	35.31±13.43*
TCE 500 mg+PCC (B)	72±4.30	56.48±5.50*	15.52±5.22* <sup>#</sup> <sup>NS</sup>	21.49±6.88* <sup>#</sup> <sup>NS</sup>
PCC (C)	71±4.47	59.5±7.42*	11.5±6.51* <sup>NS</sup>	16.19±9.14 <sup>NS</sup>
Placebo (D)	66.4±6.95	58.8±7.30 <sup>#</sup>	7.6±9.24 <sup>NS</sup>	10.61±14.11 <sup>NS</sup>
TCE 250 mg (E)	69.76±6.74	57.06±7.06*	12.71±6.02* <sup>NS</sup>	18.08±7.79
<b>Stiffness</b>				
TCE 500 mg (A)	63.59±8.51	41.68±12.10*	21.91±8.21*	34.94±13.32*
TCE 500 mg+PCC (B)	67.24±2.95	53.76±4.71*	13.48±4.50* <sup>#</sup> <sup>NS</sup>	20.03±6.42* <sup>NS</sup>
PCC (C)	62.5±3.69	51.7±6.96*	10.8±6.30* <sup>#</sup> <sup>NS</sup>	17.28±10.11 <sup>NS</sup>
Placebo (D)	65±3.97	56.25±5.82 <sup>#</sup>	8.75±3.93 <sup>#</sup>	13.53±6.12
TCE 250 mg (E)	62.41±6.03	50.71±7.20*	11.71±3.72* <sup>NS</sup>	18.98±6.43 <sup>#</sup>
<b>Disability</b>				
TCE 500 mg (A)	57.95±8.72	37.14±13.27*	20.82±8.46*	36.82±15.54*
TCE 500 mg+PCC (B)	65.76±5.31	52.52±5.12*	13.24±5.07* <sup>#</sup> <sup>NS</sup>	19.97±6.70* <sup>#</sup> <sup>NS</sup>
PCC (C)	61.50±4.39	53.1±4.46*	8.4±5.07* <sup>#</sup> <sup>NS</sup>	13.40±7.85 <sup>NS</sup>
Placebo (D)	61.5±2.35	55±3.63*	6.5±2.86 <sup>#</sup>	10.58±4.69
TCE 250 mg (E)	56.59±3.59	46.47±5.81*	10.12±4.66* <sup>#</sup> <sup>NS</sup>	17.95±8.35 <sup>#</sup>

\*p<0.05, #p<0.01, \*p<0.001 compared to baseline. Absolute change: WOMAC score - \*A versus D, A versus C, A versus E, B versus D, C versus D, D versus E (p<0.001), #A versus B, B versus C (p<0.01), NSB versus E, C versus E (p=NS), KSI - \*A versus C, A versus D, B versus D, D versus E (p<0.001), #A versus E, B versus C, C versus E (p<0.01), #A versus B, C versus D (p<0.05), Pain - \*A versus B, A versus C, A versus D, A versus E, B versus D (p<0.001), #B versus C (p<0.05), NSC versus D, B versus E, C versus E, D versus E (p=NS), Stiffness - \*A versus B, A versus C, A versus D, A versus E, B versus D (p<0.001), #D versus E (p<0.05), NSB versus C, B versus E, C versus D, C versus E (p=NS), Disability - \*A versus B, A versus C, A versus D, A versus E, B versus D (p<0.001), #B versus C (p<0.01), #D versus E (p<0.05), NSC versus D, B versus E, C versus E (p=NS), Mean percentage change: WOMAC score - \*A versus D, A versus C, A versus E, B versus D, C versus D, E versus D (p<0.001), #A versus B, B versus C (p<0.01), NSB versus E, C versus E (p=NS), KSI - \*A versus C, A versus D, D versus E (p<0.001), #A versus E, B versus C, C versus D, C versus E (p<0.01), #A versus B (p<0.05), NSB versus E (p=NS), Pain - \*A versus B, A versus C, A versus D, A versus E (p<0.001), #B versus D (p<0.01), #B versus C (p<0.05), NSC versus D, B versus E, C versus E, D versus E (p=NS), Stiffness - \*A versus B, A versus C, A versus D, A versus E, B versus D (p<0.001), #E versus D (p<0.05), NSB versus C, B versus E, C versus D, C versus E (p=NS), Disability - \*A versus B, A versus C, A versus D, A versus E, B versus D (p<0.001), #B versus C (p<0.01), #E versus D (p<0.05), NSC versus D, B versus E, C versus E (p=NS). TCE: *Terminalia chebula* extract, PCC: Proprietary chromium complex, mWOMAC: Modified Western Ontario and McMaster Universities Arthritis Index, KSI: Knee swelling index

## CONCLUSION

In this study, all the treatment groups were homogeneous in baseline characteristics. Treatment with TCE 500 mg twice daily, a combination of TCE 500 mg twice daily and the PCC 400 µg once daily, the PCC 400 µg once daily, and TCE 250 mg twice daily for a period of 12-week in subjects with joint discomfort have shown a significant reduction in mWOMAC score, KSI, VAS for pain, stiffness, and disability when compared to baseline and the placebo. Both TCE and the PCC, when given individually, have shown reductions in the efficacy variables, but the predicted synergism of their combination was not observed. Further, TCE 500 mg twice daily group produced a highly significant reduction in outcome parameters both statistically and clinically as compared to all other treatment groups. The number of rescue medication used was the least by this group. In addition, the efficacy of TCE in reducing joint discomfort appears to be dose-dependent.

The safety laboratory parameters were within normal limits at the end of the study. All the study medications were well tolerated and no serious adverse events were observed, and none of the patients have discontinued the study due to any adverse event. It was interesting to note that TCE was devoid of significant GI side effects, which are normally observed with the use of NSAIDs. Further studies with TCE in OA and other painful rheumatologic conditions are needed to confirm their therapeutic potential.

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