CLINICAL EVALUATION OF ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES OF *CURCUMA LONGA* EXTRACT IN PATIENTS SUFFERING FROM OSTEOARTHRITIS OF KNEE(S) - AN OPEN LABELED, MULTI-CENTRIC, INTERVENTIONAL, PROSPECTIVE STUDY

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Abstract: -

Background: *Curcumin, the principal curcuminoid in turmeric, is a biologically active phytochemical which may exert a chondroprotective effect through actions such as anti-inflammatory, anti-oxidative stress and anti-catabolic activity that are critical for mitigating OA disease pathogenesis and symptoms. A proprietary water-soluble turmeric extract of Curcuma longa standardized to not less than 23% total Curcuminoids (AQUATURM®) was studied for its anti-inflammatory & analgesic activity.*

Objective: *The objective was to evaluate efficacy and safety of Curcuma longa Extract in patients suffering from osteoarthritis of knee(s).*

Methodology: *After the ethics committee's approval and subsequent CTRI registration, 21 patients suffering from OA attending OPD of the study center and who consented, were enrolled in the study after all necessary investigations. Subjects were advised to take Curcuma longa extract 900 mg (prepared as powder packets) dissolved in water and consumed daily for a period of 90 days. After the baseline visit, subjects were called for follow-up visits on 30, 60, 90 days. All the subjects were closely monitored for any adverse events/ adverse drug reactions starting from the baseline visit.*

Results:

The improvement in efficacy assessment parameters such as VAS Score of Knee(s) pain, WOMAC combined score, WOMAC Pain score, WOMAC Stiffness score and WOMAC Difficulty score was statistically significant ($p < 0.05$). At the end of study (90 days) the time taken to walk 50 feet was observed to be 20.18 ±3.02 sec which was found to be statistically significant. The study product was found to be safe and well tolerated.

Conclusion: *It can be concluded that this proprietary Curcuma longa extract is a safe and effective natural supplement option for the management of osteoarthritis.*

Keywords: - *OA disease, Osteoarthritis, Turmeric, Curcuma longa*

INTRODUCTION:

Osteoarthritis (OA), especially affecting the knee joints, is a chronic degenerative joint disorder with high prevalence and is the leading cause of disability in the elderly population. The characteristic pathology involves the whole joint, including cartilage degradation, bone tissue damage, osteophyte formation, and synovial inflammation leading to symptoms like pain, stiffness, swelling and loss of normal joint functions[1]. OA is considered to bea major health condition with high prevalence rates, involving economic cost and adverse implications on the quality of life and health of a large population.[2, 3]

In the present day there seems to be no known cure for OA and the goals of management include those which reduce abnormal stresses caused on the affected joints, restore joint alignment, strengthen the surrounding muscles and provide relief from pain and muscle spasm[4]. Both pharmacological and mechanical means are used for providing relief from pain and discomfort to these patients. Alternative and complementary therapies along with exercise regimens are also widely used for managament[5]. Use of Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) such as such acetaminophen, aspirin or ibuprofen are commonly prescribed by physicians to provide relief[6]. NSAIDs carry a dose-related risk of gastrointestinal, cardiovascular, hepato-toxicity and other potentially serious toxicities, requiring caution in their use.[7-12]

Turmeric (*Curcuma longa*) is an herb used since ancient times for the treatment of various joint disorders. The principal, biologically active phytochemical constituent in Turmeric viz. curcuminoids are the most active component in turmeric.[13-14] In-vitro studies suggests that curcumin may exert a chondro-protective effect through its anti-inflammatory, anti-oxidative and anti-catabolic activity that are critical for the successful management of OA.[15]

The study product contains a proprietary water-soluble turmeric extract standardized to not less than 23% total Curcuminoids. A clinical study entitled "Clinical evaluation of anti-inflammatory and analgesic activities of *Curcuma longa* extract in subjects suffering from Osteoarthritis of Knee(s) - An Open Labeled, Multi-center, interventional, Prospective Study" was planned to evaluate efficacy and safety of *Curcuma longa* extract in patients suffering from osteoarthritis of knee(s).

Materials & Methods:

- Study design, sites -

This Open labeled, multi-centric, non-comparative, interventional, prospective clinical study was carried out in India at Sane Guruji Hospital, Malwadi, Hadapsar, Pune, Maharashtra State.

- Ethical considerations-

Ethical approval from Institutional Ethics Committee of the study center was obtained and the study was registered with Clinical Trials Registry-India (CTRI) with registration number CTRI/2021/01/030482 dated 15th January 2021.

- Enrolment of patients-

Patients suffering from OA attending outpatient department of the study center and who consented were considered for the study.

- Study duration & Visits:

The total duration of the study treatment was 3 months (90 days). Patients were asked to visit study site on monthly basis for 3 months. Patients were evaluated on every 30th day for clinical examination and various scales. Study visits included Screening visit (day -3), baseline visit (day 0), visit1 (day 30), visit 2 (day 60), visit 3 (day 90).

- Inclusion Criteria-

Patients of either sex in the age group of 30 to 65 years (both inclusive) having history of knee pain due to osteoarthritis, requiring use of NSAIDs, Acetaminophen or another analgesic agent and OA confirmed by clinical and radiological evidence on ACR diagnostic criteria (American College of Rheumatology) for the osteoarthritis of the knee(s), pain greater than or equal to 40 on Visual Analogue Scale (VAS) were included in the study. Also, patients who voluntarily provided written informed consent and willingly followed procedures as per the study protocol were included in the study.

- Exclusion Criteria:

Subjects with other conditions of knee joints like rheumatoid arthritis, gout, pseudo gout, Paget's disease of bone, chronic pain syndrome, fibromyalgia or another major joint disease, subjects with history of surgery of the study knee joint in the six months prior to the screening visit, subjects requiring knee arthroplasty within 6 months of screening or anticipating any need for a surgical procedure on the index joint during the study, subjects with signs of clinically important active inflammation of the study knee joint at the screening and/or baseline visits, subjects using systemic corticosteroids within 2 months of screening or intra-articular visco-supplementation within the past 3 months, subjects with any other investigational drug within 1 month prior to randomization, subjects with uncontrolled diabetes mellitus and hypertension, subjects with known tuberculosis, HIV, ischemic heart disease, cancer, kidney failure, pregnant and lactating women were excluded from the study. Subjects with significant abnormal laboratory parameters, known hypersensitivity to turmeric, and other conditions, which in the opinion of the investigators, make the patient unsuitable for enrollment and ability to follow the study procedures were excluded from the study.

- Laboratory & Radiological Investigations:

Investigations such as CBC, ESR, Hb%, BSL Fasting, Liver Function Tests, Lipid Profile, Renal Profile, HIV I & II, Urine Routine and Microscopic evaluation were done. Serum Uric Acid, RA test were also performed.

- Sample size:

A total 37 subjects were screened in the study of which there were 21 completers (Evaluable cases). The CONSORT flow diagram shows the complete enrollment, allocation, follow-up and analysis scenario of the study (Figure 1).

- Details of Intervention-

The study product (AQUATURM®) is a proprietary extract of herb – *Curcuma longa* rhizome. The extract is miscible / soluble in water, which enhances its bio-availability. Subjects were advised to take 900 mg of *Curcuma longa* extract dissolved in water and consumed daily for a period of 90 days.

Parameters of Assessment and their methods:

A) Assessment of Efficacy Parameters:

1) **Assessment of change in VAS Score of Knee(s) pain:** Subject's knee joint(s) pain was assessed on Visual Analogue Scale (VAS) on every follow up visit. Change in VAS score of knee pain of each was compared to baseline value.
2) **Assessment of change in WOMAC score:** Subject's knee joint(s) pain sub score, stiffness sub score and physical function sub score was assessed using WOMAC Index. Changes in WOMAC sub scores and total WOMAC score on each visit was compared to baseline score.
3) **Assessment of time required to walk 50 feet on flat surface:** Subjects were asked to walk a distance of 50 feet on flat surface and the time required was recorded and the change in at each visit was compared to baseline visit.
4) **Assessment of use of any NSAID drug as rescue medicine:** Subjects were allowed to take tab Paracetamol (up to 2 gm/day) or any standard analgesic drug in case of severe joint pain as rescue medication. No of subjects requiring rescue medications were assessed on each visit and were compared to baseline visit.
5) **Knee joint swelling on graded scale**: The knee(s) was evaluated for soft tissue swelling/synovitis (grade: 0= None, 1= Mild, 2=Moderate, 3=Severe.) on each visit. Change in soft tissue swelling/synovitis on each visit was compared to baseline visit.
6) **Assessment of overall efficacy on CGI-I:** CGI-I is a global assessment scale used by physician/investigator to provide a brief, stand- alone assessment of the Subject's global functioning prior to and after initiating a study medication, including a knowledge of the Subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the Subject's ability to function.
7) **Assessment of Subject's Global evaluation for overall change**: The subject rated the total change, whether or not, it was entirely due to the intervention with the study product compared to his/her condition at admission to the study and how much has that changed.
8) **Assessment of tolerability of study drug by investigator and subject at the end of treatment**: Evaluation of Adverse Events/Adverse Drug Reactions at every follow up visit and establishment of their relationship with the study product was assessed as post-treatment assessment of tolerability. The tolerability of extract was evaluated on safety grades as; 1= excellent overall safety (no adverse event/s reported); 2= good overall safety (mild adverse events (s) reported which subside with or without medication); 3= fair overall safety (moderate to severe adverse event(s) reported which subside with or without medication and do not necessitate stoppage of study treatment); and 4= poor overall safety (severe or serious adverse event(s) which necessitate stoppage of study.

B) Assessment of Safety: Safety was assessed by clinical review of all safety parameters, including , Adverse event reporting, vital signs, allergic reactions, Laboratory parameters including complete blood count (CBC), ESR, Hb%), Liver function tests (LFT), Renal function tests (RFT) and assessment of overall safety and tolerability of the study drug by the physician and subject on global assessment scale by the investigator and by subject himself.

- **Plan for statistical analysis**

The study data generated and collected was put to statistical analysis to determine final results and conclusions. Demographic data are presented in tables and graphs. Data on discrete variables has been represented as n (%). Data on continuous variables has been represented as mean (SD). GraphPad InStat Version 3.6 (www.graphpad.com) software was used for statistical analysis of data. P-Value < 0.05 was considered significant. For continuous data – Intra-group comparison, Paired t-test, Wilcoxon matched-pairs signed-ranks test were used.

Results:

In the present study a total of 37 subjects were screened. There were 16 screen failures. Total 21 subjects were included in the study and they received allocated study medicine. There were no dropouts in the study and 21 subjects were considered as completers.

The mean age of the subjects enrolled in the study was 55.28 ±8.08 years. There were a total of 04 (19.04%) males and 17 (80.95%) females in the study. The average weight and BMI of the subjects in the study was 64.85 ±10.89 kg and 25.19 ±3.96 respectively. 06 subjects (28.57%) in the study had Hypertension while none had Diabetes. Serum Uric acid was observed to be 5.62 ±1.35 i.e. within normal range at baseline as none of the subjects had high uric acid. None of the subjects had positive serology test for Rheumatoid Arthritis.

Primary Objective:

Assessment of change in VAS Score of Knee(s) pain:

The average VAS Score at the baseline was 79.76 ±9.80, which significantly ($p < 0.05$) reduced to 70.47 ±11.71 at the end of 30 days. At the end of 60 days, the VAS Score further reduced to 66.66 ±11.97 while at the end of 90 days it was observed to be 60 ±12.44 which was significantly less ($p < 0.05$) as compared to baseline.

The average WOMAC combined score at the baseline was 32.80 ±11.07. This significantly ($p < 0.05$) reduced to 28.38 ±8.17 at the end of 30 days. At the end of 60 days, the WOMAC combined score further reduced to 26.52 ±8.47 while at the end of 90 days it was observed to be 24.57 ±8.24 which was significantly less ($p < 0.05$) as compared to its baseline.

The average WOMAC Pain score at the baseline was 6.76 ±1.78. This significantly ($p < 0.05$) reduced to 5.80 ±1.86 at the end of 30 days. At the end of 60 days, the WOMAC Pain score further reduced to 5.23 ±1.48 while at the end of 90 days it was observed to be 4.66 ±1.59 which was significant ($p < 0.05$) as compared to its baseline reading.
The average WOMAC Stiffness score at the baseline was 3.14 ±1.15. This significantly ($p < 0.05$) reduced to 2.61 ±1.07 at the end of 30 days. At the end of 60 days, the WOMAC Stiffness score further reduced to 2.52 ±1.07 while at the end of 90 days it was observed to be 2.14 ±0.91 which was significantly less ($p < 0.05$) as compared to its baseline reading.
The average WOMAC Difficulty score at the baseline was 22.90 ±9.09. This significantly ($p < 0.05$) reduced to 19.95 ±6.74 at the end of 30 days. At the end of 60 days, the WOMAC Difficulty score further reduced to 18.76 ±7.36 while at the end of 90 days it was observed to be 17.76 ±6.84 which was significantly less ($p < 0.05$) as compared to its baseline reading.

Secondary Objective:

Assessment of time required to walk 50 feet on flat surface:

In the study it was found that at baseline visit the mean time required to walk 50 feet distance was 21.51 ±3.17 seconds which reduced to 21.34 ±3.20 sec and 20.74 ±2.81 sec at the end of 30 days and 60 days ($p > 0.05$) At the end of study (90 days) the time taken to walk 50 feet was observed to be 20.18 ±3.02 sec which was found to be statistically significant.
One subject required the use of rescue medication (local application of pain relieving topical product) for 6 to 8 days during the study period.
The average swelling score of Knee at the baseline was 0.80 ±0.74. This significantly ($p < 0.05$) reduced to 0.57 ±0.67 at the end of 30 days. At the end of 60 days, the swelling of Knee further reduced to 0.38 ±0.66 while at the end of 90 days it was observed to be 0.14 ±0.35 which was significant ($p < 0.05$) as compared to its baseline score.
As per global assessment for overall change by investigator, 42.86% subjects showed much improvement, while 52.38% of subjects showed minimal improvement. 4.76% subjects showed no change in Osteoarthritis condition. As per global assessment for overall change by subjects, 52.38% subjects showed much improvement, while 42.86% of subjects showed minimal improvement. 4.76% subjects showed no change in Osteoarthritis condition. None of the subjects showed worsening f their condition.

Evaluation of AE/SAE (Safety Evaluation):

Out of 21 Subjects evaluated, 5 Subjects were reported to have 5 AEs. The common AE reported in the subjects were Wrist joint pain (due to physical injury), Fever, Headache, Cold and running nose. These adverse events were found to be unrelated to the study product or procedure. There was no requirement of interruption of the study product or procedure to resolve these episodes. Out of 21 Subjects evaluated, 02 Subjects were reported to have SAEs. Both the SAE were Covid-19 Positive and these subjects were required to be hospitalized. These SAEs were unrelated to the study drug or procedure.

Discussion:

The study was conducted to evaluate anti-inflammatory and analgesic activities of a proprietary *Curcuma longa* extract in subjects suffering from Osteoarthritis of Knee(s). The study population was primarily of individuals above the age of 50 years with an average age of 55.28 ±8.08 years. More females than males (4 females/17males) were part of the study. These findings are in line with the available literature that women are more commonly affected and burdened by osteoarthritis compared to men[16]. The participating subjects had a higher-than-normal BMI of 25.19 ±3.96 showing the relationship of higher body weight and occurrence of OA.
Three months of consumption of a proprietary *Curcuma longa* extract significantly reduced knee joint pain as assessed on VAS. The significant reduction in the knee joint pain started from day 30 onwards and continued further till 90 days in the study. There was 24.77% reduction in the knee joint pain at the end of the study. All the WOMAC sub-scores viz. Combined score, Pain score, stiffness score and difficulty score, significantly reduced at the end of the study. The significant reduction in all the WOMAC sub-scores started from day 30 onwards and continued further till the end of the study. There was 25.09%, 31.06%, 31.84% and 22.44% reduction in the combined WOMAC score, WOMAC Pain score, WOMAC stiffness score and WOMAC difficulty score respectively at the end of the study as compared to baseline. A significant improvement in the average time required to walk 50 feet distance was observed at the end of the study. Swelling in knee joint significantly reduced from day 30 onwards and this reduction continued till the end of the study. There was 82.5% reduction in the knee joint swelling at the end of the study.
These results suggest that water soluble turmeric extract of *Curcuma longa* standardized to not less than 23% total Curcuminoids is significantly effective in reducing joint pain, swelling, stiffness and difficulty in joint movements. Curcumin has been extensively studied in arthritis and has its exhibited therapeutic benefits as a potential anti-inflammatory supplement. Several studies showed its action on down-regulating various inflammatory markers like phospholipase A2, cyclooxygenase-2, lipoxygenases, PGEs and reducing TNF-Alpha-and interleukins such as IL-1b, IL-6, and IL-8. It also acts as inducer of apoptosis in synoviocytes decreasing the inflammation process[17]. It has also been established in research studies that Curcumin possesses analgesic activity[18]. Curcumin protects human chondrocytes from IL-1 -induced inhibition of collagen type II[19]. Curcumin has also been used as an Immuno-modulator, rejuvenator and anti-oxidant· Agent[20] It can thus be said that through these multiple actions *Curcuma longa* extract effectively relieves symptoms of Osteoarthritis.
This proprietary *Curcuma longa* extract was found to be safe as vital parameters like pulse, respiratory rate, body temperature, systolic and diastolic blood pressure remained in the normal range throughout the study period. Also, there

was no significant change in the levels of safety related laboratory parameters. One of the additional findings in the study was a significant reduction in the lipid levels like Serum Triglycerides, LDL and VLDL cholesterol while an increase in the protective lipid HDL was observed. These results indicate that *Curcuma longa* extract is safe to use in subjects suffering from Osteoarthritis of knee joint.

Conclusion:

Three months of consumption of a proprietary *Curcuma longa* extract (AQUATURM®) showed significant reduction in joint pain, joint swelling and joint stiffness in patients suffering from Osteoarthritis. Also, significant improvement in mobility of joints of the knee(s) was evident after three months of consumption of this extract. Additional findings were a reduction in lipid levels and a significant increase in HDL levels providing evidence of the protective effects of *Curcuma longa* extract. It can be concluded that this proprietary *Curcuma longa* extract is a safe and effective natural supplement option for the management of osteoarthritis. Further controlled studies on larger sample size are warranted to establish and validate the effects of *Curcuma longa* extract in cases of musculoskeletal disorders like Osteoarthritis.

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