CLINICAL EVALUATION OF ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES OF AQUATURM® (BRANDED EXTRACT OF CURCUMA LONGA) IN INDIVIDUALS DIAGNOSED WITH KNEE JOINT PAIN CAUSED BY OSTEOARTHRITIS– A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL STUDY

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Abstract:

Background: *Anti-inflammatory and analgesic activities of Curcuma longa extract can support in the management of knee joint pain caused by osteoarthritis.*

Objectives: *Evaluation of anti-inflammatory and analgesic activities of AQUATURM® (branded extract of Curcuma longa) in individuals diagnosed with knee joint pain caused by osteoarthritis.*

Methods: *60 participants diagnosed with knee osteoarthritis were randomized in two groups through a double-blinded procedure. Of these, 56 subjects completed the study (26 in AQUATURM® group and 30 in placebo group). AQUATURM® or its matching placebo was given in a dose of 1 capsule of 250 mg twice daily after meals for 90 days. Assessment of comparative change in knee joint pain on VAS, and WOMAC Index was performed in monthly intervals. Other parameters included time to walk 50 feet, use of painkillers as rescue medication, changes in the CRP levels, and safety assessment through adverse event monitoring and laboratory parameters was performed.*

Results*: A significant reduction ($p<0.05$) in pain was observed on the VAS scale with the use of AQUATURM® (55.77 ±15.98 to 46.38 ±16.17) as compared to placebo (56.67 ±17.02 to 50.93 ±14.88) over a period of 90 days. On the WOMAC index, a significant reduction ($p<0.05$) was observed on the domains of pain (10.92±3.37 to 7.73 ±3.59 in AQUATURM® group and 10.90 ±3.16 to 9.76 ±3.81 in placebo group) and stiffness (4.80 ±1.60 to 2.88 ±1.58 in AQUATURM® group and 4.50 ±1.43 to 4.36 ±2.00 in placebo group). A significant reduction was observed on CRP levels (4.97 ±1.59 to 2.68 ±0.88 with AQUATURM® and 4.93 ±1.99 to 4.19 ±2.81 with placebo). AQUATURM® did not produce any significant adverse effects on clinical and laboratory parameters. AQUATURM® was well tolerated.*

Conclusion*: Supplementation of AQUATURM® in individuals diagnosed with knee osteoarthritis showed significant reduction in pain, stiffness and swelling showing its analgesic and anti-inflammatory effect.*

Keywords*: AQUATURM®, Osteoarthritis, Curcumin, knee joint pain, inflammation, turmeric, supplement, pain, anti-inflammatory.*

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative joint disorder of high prevalence that remains the leading cause of disability in elderly people. OA is amongst the most prevalent & disabling chronic conditions commonly affecting knees, hands, hips, spine, and feet. This multifactorial disease is characterized by destruction of the articular cartilage, sub-chondral bone alterations, synovitis, joint pain & tenderness, limitation of movements, occasional effusion, and variable degrees of local inflammation without systemic manifestations.[1,2,3] The high prevalence rates, economic cost & adverse implications on the quality of life & health state make OA a major public health issue.[4, 5]

Since there is no known cure for OA, the goals of management of the disease are to reduce abnormal stresses on the affected joints, restore joint alignment, strengthen muscles, and treat pain and muscle spasm. Pain relief is the priority of most of the patients. Both pharmacological and mechanical means are used[6]. Treatment may include exercise, analgesics such as acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen.[7] NSAIDs carry a dose-related risk of gastrointestinal distress, [8,9] cardiovascular distress[10-13], hepatotoxicity[14], and other potentially serious toxicities, requiring caution in their use. Alternative and complementary therapies have also been extensively used for the management of pain in OA.[15]

Many herbs such as turmeric have been used for centuries for the management of osteoarthritis and various joint disorders. Curcumin, the principal curcuminoid and the most active component in turmeric, is a biologically active phytochemical.[16] Evidence from recent in-vitro and in-vivo studies suggests that curcumin 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.[17]

AQUATURM® is a proprietary turmeric extract developed by Lodaat Pharma, which achieves superior bioavailability while using less product per serving and contains water soluble turmeric extract standardized to not less than 23% total Curcuminoids. The present study evaluates the effect of AQUATURM® for its analgesic and antiinflammatory activity in individuals diagnosed with knee Osteoarthritis The statements in this presentation have not been evaluated by the Food and Drug Administration. These products are not meant to diagnose, treat, cure, or prevent any diseases.

Materials & Methods:

Settings and locations:

The study was conducted at the following study sites –

1. Ayurved Seva Sangha, Ayurved Mahavidyalaya, Nashik, Maharashtra state, India.
2. Shri. Gurudeo Ayurved College, Amravati, Maharashtra state, India
3. National Institute of Ayurveda, Jaipur, Rajasthan State, India.

Study design:

The study was a randomized, double blind, placebo controlled, comparative, interventional, prospective clinical study.

Ethical considerations:

The study was approved by the Institutional Ethics Committee all the three sites and registered with Clinical Trial Registry - India (CTRI/2021/08/035416 [Registered on: 04/08/2021]). The study was carried out and reported adhering to the CONSORT statement.

Study duration & Visits:

The total duration of the study was 90 days, during which the study products were administered. The study products (either placebo or AQUATURM®) were administered in a dose of 1 capsule of 250 mg twice daily after meals, to be orally ingested with water. Participants were followed up at regular monthly intervals (Baseline, 30 days, 60 days and 90 days) to record efficacy and safety parameters.

Eligibility criteria for participants:

Inclusion Criteria:

Participants of either gender, in the age group of 30-65 years diagnosed with osteoarthritis of either or both the knee joints on ACR criteria (clinical + Radiological) were included in the study. At the time of screening a VAS (Visual Analogue Scale) score of 40 or more was considered for inclusion.

Exclusion Criteria:

Participants with rheumatoid arthritis, gout, pseudo gout, inflammatory arthritis, Paget's disease of bone, chronic pain syndrome, fibromyalgia or any other major joint disease were excluded from the study. Individuals with a history of surgery, including arthroscopy or major trauma to the knee joint in the previous six months were excluded. Participants using systemic corticosteroids within 2 months of screening, or intraarticular visco supplementation within 3 months prior to the beginning of the trial were not considered for the study. Participants with uncontrolled diabetes mellitus and/or hypertension, known cases of tuberculosis, HIV, ischemic heart disease, cancer, kidney failure, significant abnormal laboratory parameters, and known hypersensitivity to turmeric were excluded from the study. Other conditions, which in

the opinion of the investigators, could have made participants unsuitable for enrolment or could have interfered with their participation were also excluded from the study.

Laboratory Investigations:
All the participants in the study were asked to undergo laboratory investigations including C-Reactive Protein (CRP), CBC, Renal Profile, Liver Profile, Blood Sugar Fasting and Lipid Profile at baseline (day 0) and at the end of the study (Day 90). X-Ray of the affected Knee joint was conducted at baseline and at the end of the study.

Randomization:
Block randomization with center as the stratum was performed. Participants meeting eligibility criteria were randomized 1:1 to one of the two groups (AQUATURM® Group of Placebo Group).

Intervention Details:
Participants in the two groups were randomly assigned to either receive AQUATURM® or a matching placebo. AQUATURM® contains standardized extract of the Curcuma longa standardized to contain not less than 23% total curcuminoids. Placebo capsules were prepared using Micro Crystalline Cellulose Powder.

Primary and secondary outcome measures:
Primary outcome measures were comparative change in pain on Visual Analogue Scale
(VAS) for the knee joint from baseline to 90 days and between the two groups (AQUATURM® and Placebo). Another primary outcome measure was comparative change in the pain, stiffness, difficulty and combined WOMAC score for OA from baseline to 90 days and between the two groups.
Secondary outcome measures were comparative change in time to walk 50 feet, requirement of rescue medicines (NSAID's) and swelling of the knee joint. CRP levels were also measured at baseline and at the end of 90 days in both the groups. Overall tolerability was assessed based on adverse events both clinically and on laboratory parameters.

Study methodology:
After the ethics committee's approval & subsequent registration of the study on CTRI, participants were enrolled in the study. On the screening visit, a written informed consent was obtained. On baseline visit (Day 0), participants meeting the inclusion/exclusion criteria were randomized in either of the two groups who were advised to take given product in a dose of 1 capsule (250 mg) twice daily after meals with water for 90 days.

Knee joint(s) pain was assessed on Visual Analogue Scale (VAS). The qualified knee(s) were recorded as the index joint and was not changed thereafter during the study period. Participants underwent investigations such as RA Test (to rule out rheumatoid arthritis), Serum Uric Acid (to rule out Gout), and X-Ray imaging (anterior-posterior view and lateral view) of Index/selected knee. OA of knee was confirmed by radiographs and diagnosed according to ACR diagnostic criteria (clinical+ radiological).

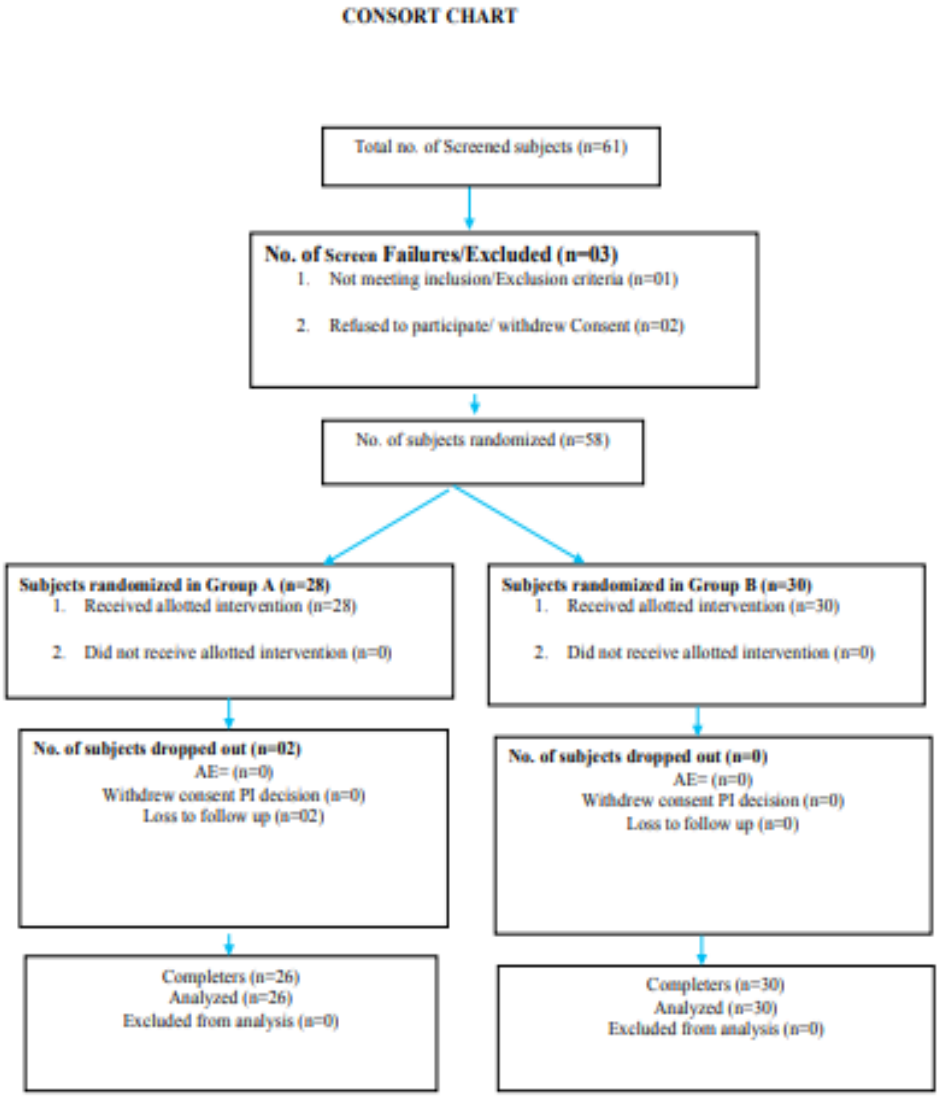
Laboratory investigations included fasting blood sugar, CRP, CBC, ESR, Hb%, liver function tests, renal function tests, and lipid profile. Subjects who had been taking any other OA supplement were required to undergo a 7-day washout period. During the washout period, and during the study itself, participants were advised to refrain from NSAIDs or any other local or systemic analgesics and steroids except if required as rescue medication.

At baseline (day 0) and at every monthly follow up (day 30, day 60 and day 90) participant's Knee joint(s) pain was assessed on Visual Analogue Scale (VAS). Participant's joint pain sub score, stiffness sub score and physical function sub score were assessed on the WOMAC Index. Knee(s) was evaluated for soft tissue swelling/synovitis (grade: 0= None, 1= Mild, 2=Moderate, 3=Severe.) Participants were asked to walk 50 feet on flat surface and the time required was recorded.

On day 90, laboratory investigations, CRP, CBC, ESR, Hb%, Blood sugar fasting, Liver function tests, renal function tests, and lipid profile were performed. X-ray index knee joint (AP and lateral view) was performed. Tolerability and adverse effects were assessed clinically and in laboratory results at the end of the study.

Plan for statistical analysis:
The data were analyzed for central tendencies (mean, median), range, standard error, and standard deviation. Data were tabulated and graphically shown using standard format and MS Excel. Statistical tests were carried out to compare study groups as per the distribution (normality) Student's T test (normative), Mann-Whitney statistic (nonparametric), Chi-square statistic (categorical), ANOVA. The level of significance at $p<0.05$ (two sided) was considered significant. Both intent-to-treat and per protocol completer analysis were performed as applicable. Standard statistical software programs were used (GraphPad InStat Version 3.6).

Results –
61 subjects were screened and 58 were randomized in the study of which 56 were considered completers (Evaluable cases). Out of these 56 subjects, 26 subjects were in the AQUATURM® Group and 30 subjects were in placebo group.
Details provided in the consort chart



Baseline demography –

There was no significant difference in the age and gender distribution of participants in the study. The average age of subjects in AQUATURM® group was 54.65 ±9.03 years while in placebo group it was 50.17 ±9.24 years. There were 19 (73.08%) Females and 7 (26.92%) males in the AQUATURM® group while the respective number were 23 (76.67%) and 7 (23.33%) in the placebo group. The mean weight and BMI of the subjects in AQUATURM® group was 65.70 ±11.60 kg and 26.37 ±4.68 Kg/m^2 respectively while in placebo group it was 64.56 ±10.49 kg and 26.53 ±4.38 Kg/^{m2,} respectively. *Details in Table 1.*

Table 1: Baseline Demography in the two study groups

		AQUATURM® Group (n=26)	Placebo Group (n=30)
Gender	Female	19 (73.08%)	23 (76.67%)#
	Male	07 (26.92%)	7 (23.33%)#
Age in Years		54.65 ±9.03	50.17 ±9.24#
Height in Meter		1.58 ±0.05	1.56 ±0.068#

Weight in Kg	65.70 ±11.60	64.56 ±10.49[#]
BMI (Kg/m^2)	26.37 ±4.68	26.53 ±4.38[#]
Sr. Uric Acid	4.70 ±1.11	4.7 ±1.13[#]
BSL Fasting	119.65 ±59.34	108.88 ±45.66[#]

[#]indicates a $p>.05$

Assessment of Knee joint pain on VAS-

There was a significant reduction in pain as measured on VAS scale from baseline to monthly follow up visits with the use of AQUATURM® as compared to placebo. The average pain measured on VAS reduced from 55.77 ±15.98 at baseline to 46.38 ±16.17 at the end of 90 days in AQUATURM® group the reduction in placebo group was observed from 56.67 ±17.02 at baseline to 50.93 ±14.88. *Details in Table 2.*

Table 2: Assessment of changes in knee Joint Pain on VAS

		AQUATURM® Group (n=26)	Placebo Group (n=30)	P-Value Between Groups
Knee Joint Pain on VAS scale	Baseline Visit	55.77 ±15.98	56.67 ±17.02	
	Day 30	51.65 ±16.10**	53.07 ±15.38	0.08791
	Day 60	48.85 ±15.88**	52.53 ±17.15	0.0877
	Day 90	46.38 ±16.17**	50.93 ±14.88*	0.0478*

*P-value ≤0.05, **= P-value ≤0.01

Assessment of Pain, Stiffness, Difficulty score on WOMAC Index-

AQUATURM® use showed a significant reduction in the pain score on WOMAC index as compared to placebo where the score reduced from 10.92±3.37 to 7.73 ±3.59 in 90 days while in placebo this reduction was observed to be from 10.90 ±3.16 at baseline to 9.76 ±3.81. A significant reduction in the Stiffness score on WOMAC index was observed with the use of AQUATURM® as compared to placebo where the score reduced from 4.80 ±1.60 to 2.88 ±1.58. In the placebo group this reduction was observed to be marginal from 4.50 ±1.43 to 4.36 ±2.00.

A non-significant reduction was observed in the combined WOMAC score between the placebo group and AQUATURM® group. WOMAC combined score at the baseline visit was 48.77 ±13.77 in AQUATURM® which significantly reduced to 38.00 ±14.56 at the end of Day 90, while in the placebo group the average WOMAC combined score reduced from 50.6 ±12.13 to 45.93 ±11.56 at Day 90. A non-significant reduction was observed in difficulty score on WOMAC index where the score at baseline in AQUATURM® was observed as 32.23±11.34, which significantly reduced to 26.42 ±10.58. In the placebo group this reduction was from 33.33 ±10.16 at baseline to 28.10 ±12.29 at Day 90. *Details in table 3.*

Table 3: Assessment of Changes in WOMAC Index

		AQUATURM® Group (n=26)	Placebo Group (n=30)	P-Value Between Groups
WOMAC Combine Score	Baseline Visit	48.77 ±13.77	50.6±12.13	
	Day 30	44.42±14.25**	49.07±12.46	0.0725
	Day 60	40.92±13.77**	48.30±12.45	0.0924
	Day 90	38±14.56**	45.93±11.56	0.0831
WOAMC Pain Score	Baseline Visit	10.92±3.37	10.90±3.16	
	Day 30	10.92±3.37	10.96±3.84	0.4845
	Day 60	9.65±3.39	9.53±4.44	0.8572
	Day 90	7.73±3.59*	9.76±3.81	0.049*
WOAMC Stiffness Score	Baseline Visit	4.80±1.60	4.5±1.43	
	Day 30	3.42±1.60*	4.63±1.75	0.0701
	Day 60	3±1.52*	4.43±1.83	0.3328
	Day 90	2.88±1.58*	4.36±2.00	0.0322*
WOAMC Difficulty Score	Baseline Visit	32.23±11.34	33.33±10.16	
	Day 30	29.69±10.88*	32.80±11.09	0.8352
	Day 60	27.81±10.02*	30.40±11.14	0.8868
	Day 90	26.42±10.58*	28.10±12.29*	0.0917

Assessment of time to walk 50 feet

A non-significant difference on the average time to walk 50 feet was observed with the use of AQUATURM® as compared to placebo. The mean time required to walk 50 feet distance was 32.42 ±16.70 (sec), which reduced to 29.69 ±15.48 at the end of 90 days with the use of AQUATURM® while in placebo group the same reduced from 32.17 ±15.18 (sec) to 31.50±14.69 at the end of 90 days. *Details in Table 4*.

Table 4: Assessment of changes in time to walk 50 feet on flat surface

		AQUATURM® Group (n=26)	Place bo Group (n=30)	P-Value Between Groups
Time required to walk 50 feet on flat surface (Seconds)	BaselineVisit	32.42 ±16.70	32.17±15.18	
	Day 30	31.23 ±16.23	31.27±14.41	0.8414
	Day 60	31.31 ±16.27	31.20±13.79	0.9058
	Day 90	29.69±15.48**	31.50±14.69	0.0918

*P-value ≤0.05, **= P-value ≤0.01

Assessment of knee joint swelling

A significant reduction in average swelling was observed with the use of AQUATURM® over 90 days compared to placebo. The average swelling was recorded as 0.92 ±0.68 at baseline, which was almost absent i.e., 0.15 ±0.36 at the end of 90 days with the use of AQUATURM®. In the Placebo Group, the average swelling of knee at the baseline visit was 0.95 ±0.60, which reduced to 0.60 ±0.53 at the end of 90 days. *Details in Table 5*.

Table 5: Assessment of changes in knee joint swelling on graded scale

		AQUATURM® Group (n=26)	Placebo Group (n=30)	P-Value Bet ween Groups
Knee joint swelling on Graded scale	Baseline Visit	0.92±0.68	0.95±0.60	
	Day 30	0.30±0.47**	0.68±0.42	0.4944
	Day 60	0.15±0.36**	0.66±0.52	0.2430
	Day 90	0.15±0.36**	0.60±0.53	0.046*

P-value ≤0.05, **= P-value ≤0.01

Assessment of CRP levels

A significant reduction on Serum CRP levels was observed with the use of AQUATURM® over a period of 90 days. The mean CRP levels reduced from 4.97 ±1.59 to 2.68 ±0.88 after 90 days with the use of AQUATURM® while in the placebo arm the reduction was observed to be non-significant, from 4.93 ±1.99 to 4.19 ±2.81. *The details are presented in table 6.*

Table 6: Assessment of changes in CRP Level

		AQUATURM® Group (n=26)	Placebo Group (n=30)	P-Value Between Groups
CRPLevel	Baseline Visit	4.97 ±1.59	4.93 ±1.99	0.048*
	Day 90	2.68 ±0.88	4.19 ±2.81	

* P-value ≤0.05, **P-value ≤0.01

Other observations-

With regards to the use of rescue medications (NSAIDs) 2 participants in AQUATURM® group required it for 1 day while none of the other participants required any rescue medication during the study. Global assessment of overall change as per the investigator and the participant showed that most participants reported excellent to satisfactory overall efficacy and tolerability of AQUATURM®. A total of 9 AEs were reported in the study, out of which 5 subjects reported to have 5 AEs in AQUATURM® Group, while 4 subjects reported to have 4 AEs in Placebo Group. The AEs reported were fever and cold, acidity, nausea, weakness, somnolence, indigestion, flatulence, and abdomen discomfort. None of the AEs were related to the study products.

Assessment of effect on Vitals and Laboratory investigations showed that AQUATURM® did not produce any notable changes on the laboratory parameters like CBC, renal profile, liver profile and lipid profile over a period of 90 days. It was noteworthy that the use of AQUATURM® produced significant reduction of LDL cholesterol (Table 7).

Table 7: Assessment of changes in Lipid Profile

Parameter	AQUATURM® Group (n=23)		Placebo Group (n=26)		P value between groups
	Baseline	Visit 3	Baseline	Visit 3	
Sr. Cholesterol (mg/dL)	201.1 ±44.30	179.2 ±22.26	216.8 ±31.07	202.4 ±33.98	0.0722
Sr. Triglyceride (mg/dL)	115 ±48.35	105.9 ±34.23	123.8 ±46	117.9 ±41.28	0.3814
HDL (mg/dL)	54.73 ±15.73	65.85 ±18.04**	58.05 ±14.27	56.04 ±17.22	0.0970
LDL (mg/dL)	123.5 ±42.40	112.9 ±26.05*	131.1 ±32.77	132.6 ±36.25	0.0476*
VLDL (mg/dL)	22.91 ±9.77	20.97 ±6.98	31.45 ±37.21	33.62 ±9.23	0.3933
TC: HDL	4.96 ±4.28	3.20 ±1.02**	4.03 ±1.60	4.25 ±1.22	0.05*

* = P-value ≤0.05 **= P-value ≤0.01

Discussions –

The results of the study demonstrate that AQUATURM® i.e., extract of turmeric given in a dose of 250 mg twice daily for a period of 90 days has significant analgesic and antiinflammatory activities as observed in the reduction of pain, stiffness and swelling of knee joints.

Curcumin has been extensively studied in several types of arthritis and has exhibited therapeutic effect in osteoarthritis. Understanding the mechanism of action of Curcumin, it has been seen in several studies to down-regulate phospholipase A2, cyclooxygenase-2, lipoxygenases, PGEs and reducing TNFa-and interleukins such as IL-1b, IL-6, and IL-8. It also acts as inducer of apoptosis in synoviocytes decreasing the inflammation process.[18] It has also been established in the research study that Curcumin possesses analgesic activity.[19] Curcumin protects human chondrocytes from IL-1 -induced inhibition of collagen type II and 1.[20] Curcumin has also been used as an immunomodulator[9], and anti-oxidant[21]. In the present clinical study, significant reduction in LDL level and TC: HDL was observed in AQUATURM® group compared to placebo group. Also, there was a significant increase in HDL level in AQUATURM® group compared to placebo group. Besides its analgesic and anti-inflammatory activities, curcumin may have added benefits on hyperlipidemia.

Conclusion

The study data concludes that AQUATURM® (proprietary extract of Curcuma longa) showed a significant reduction in the symptoms of osteoarthritis including joint pain, swelling, and loss or restriction of mobility(stiffness) by virtue of its analgesic and antiinflammatory effect. A significant reduction in LDL level and TC: HDL was observed in AQUATURM® group compared to placebo group. Also, there was a significant increase in HDL level in AQUATURM® group compared to placebo group. Besides its analgesic and anti-inflammatory activities, curcumin appears to have added benefits regarding hyperlipidemia. However further research should be conducted to confirm these associations

Consumption of AQUATURM® for 3 months (90 days) also did not produce any adverse effects and was well tolerated. AQUATURM® can be recommended as a safe and effective support for the management of knee joint pain caused by osteoarthritis. Further studies to understand the exact mechanism of action on large populations need to be carried out to gain a complete understanding of the mechanistic action of curcumin and its full effects upon osteoarthritis

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