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INTRODUCTION

Osteoarthritis (OA) is the most common degenerative joint disease, affecting more than 25% of the population over 18 years-old. Pathological changes seen in OA joints include progressive loss and destruction of articular cartilage, thickening of the subchondral bone, formation of osteophytes, variable degrees of inflammation of the synovium, degeneration of ligaments and menisci of the knee and hypertrophy of the joint capsule. The etiology of OA is multi-factorial and includes joint injury, obesity, aging, and heredity. OA of the knee and hip are a growing health concern and are the most common form of arthritis. Pain and disease can range from very mild to very severe. The pain in OA patients typically worsens with weight bearing, including walking and standing, and improves with rest. Due to decreased movement because of the pain, regional muscles may atrophy, and ligaments may become laxer. Morning stiffness and articular gelling after periods of inactivity are common manifestations of OA. [1]

Osteoarthritis is mainly caused by imbalance between degeneration and regeneration of articular cartilage accompanied by pathological changes of other joint structures. No generally recognizable description of the pathogenic pathway of osteoarthritis (OA) exists so far, however recent studies have widened the knowledge of the underlying pathology. Synthesis of IL-1ß and TNF-α, as well as their membrane-bound receptors, is up regulated in osteoarthritis. These cytokines are potentiators of an inflammatory cascade, stimulating their own production and that of a range of proinflammatory cytokines such as IL-6, IL-8, IL-11, IL-17 and RANTES. IL-1ß and TNF-α activity stimulates the release of nitric oxide, a molecule best known for its modulatory role in the cardiovascular system. In cartilage, nitric oxide appears to inhibit collagen and proteoglycan synthesis and increase the activity of matrix metalloproteinase. The most important long-term effect may be the induction of apoptosis of chondrocytes. Because chondrocytes are not regenerated and loss of chondrocyte mass and function further accelerates degradative processes.

OA affects about 3.3% to 3.6% of the population globally. It causes moderate to severe disability in 43 million people making it the 11th most debilitating disease around the world. The incidence of OA rises precipitously with age; as a result, the prevalence and burden of OA is increasing rapidly. This has become a worldwide problem and novel therapeutic intervention is warranted.[2]

The current management modalities are targeted towards symptom control. The most commonly used medications include acetaminophen and NSAIDs which offers temporary relief from symptoms, but fail to prevent progression of disease. Most of the NSAIDs on long term use are associated with gastric ulcers, GI bleeding and damage to kidneys. Hence there is quest for safe and effective novel therapy for the management of osteoarthritis.

Turmeric extract has been used since many years for treating osteoarthritis in traditional medicine. Curcumin, a polyphenolic compound derived from the dietary spice turmeric possesses diverse pharmacologic and biological properties. Curcumin has been known for its anti-inflammatory and antioxidant properties from many years which is beneficial in Osteoarthritis.[3]

LITERATURE REVIEW

Turmeric is a spice that has received much interest from both the medical/scientific worlds as well as from the culinary world. Turmeric is a rhizomatous herbaceous perennial plant (Curcuma longa) of the ginger family. The medicinal properties of turmeric, the source of curcumin, have been known for thousands of years; however, the ability to determine the exact mechanism(s) of action and to determine the bioactive components have only recently been investigated. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane, is the main natural polyphenol found in the rhizome of Curcuma longa (turmeric) and in others Curcuma spp. Curcuma longa has been traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer properties. Antioxidant and anti-inflammatory properties are the two primary mechanisms that explain the majority of the beneficial effects of curcumin in osteoarthritis.

Curcumin has been shown to improve systemic markers of oxidative stress. There is evidence that it can increase serum activities of antioxidants such as superoxide dismutase (SOD). Oxidative stress has been implicated in many chronic diseases, and its pathological processes are closely related to those of inflammation, in that one can be easily induced by another. In fact, it is known that inflammatory cells liberate a number of reactive species at the site of inflammation leading to oxidative stress, which demonstrates the relationship between oxidative stress and inflammation. In addition, a number of reactive oxygen/nitrogen species can initiate an intracellular signaling cascade that enhances pro-inflammatory gene expression. Inflammation has been identified in the development of many chronic diseases and conditions including arthritis.

Tumor necrosis factor α (TNF-α) is a major mediator of inflammation in most diseases, and this effect is regulated by the activation of a transcription factor, nuclear factor (NF)-κB. Whereas TNF-α is said to be the most potent NF-κB activator, the expression of TNF-α is also regulated by NF-κB. In addition to TNF-α, NF-κB is also activated by most inflammatory cytokines; gram-negative bacteria; various disease-causing viruses; environmental pollutants; chemical, physical, mechanical, and psychological stress; high glucose; fatty acids; ultraviolet radiation; cigarette smoke; and other disease-causing factors. Therefore, agents that downregulate NF-κB and NF-κB–regulated gene products have potential efficacy against several of these diseases. Curcumin has been shown to block NF-κB activation increased by several different inflammatory stimuli. Curcumin has also been shown to suppress inflammation through many different mechanisms beyond the scope, thereby supporting its mechanism of action as a potential anti-inflammatory agent. [4]

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STUDY OBJECTIVE

The objective of this clinical study to evaluate comparative clinical Efficacy and Safety of ABSOCURCUMIN (Turmeric extract) in Joint Health.

STUDY DESIGN

A randomized, double-blind, placebo-controlled clinical study

OVERALL STUDY PLAN

Subjects with Knee osteoarthritis grade II to III of Kellgren and Lawrence assessment were enrolled into study along with other inclusion/ exclusion criteria. After obtaining a written informed consent, duly approved by institutional ethics committee, subjects were randomized into one of the two treatment arms, placebo arm and active arm (Turmeric extract). All 30 subjects received either placebo or active product in the ratio of 1:1 for a period of 56 days, as one capsule twice daily after meals. The efficacy of daily doses of 500mg Turmeric extract was evaluated with that of a placebo in improving WOMAC and VAS scores after 56 days.

DOSE AND METHOD OF ADMINISTRATION

Dosage Two 500mg soft gel capsule orally in the morning after breakfast and in night post dinner

STANDARDISATION

Each capsule of 500mg Absocurcumin (Curcuma longa extract) contains Total Curcuminoids NLT 65% w/w and Turmerones NLT 2.5% w/w by HPLC Polysaccharides NLT 15% w/w by Gravimetry.

SELECTION & WITHDRAWAL OF SUBJECTS

SUBJECT SCREENING

Medical history and demographic data including sex, age, body weight (kg), and height (cm), and habits were recorded during general screening of volunteers that was organized 1 day prior to study start. Each subject underwent a complete general physical examination and laboratory tests.

INCLUSION CRITERIA

To qualify for enrollment in the study, the subject:

- Ambulatory, male and female subjects of 40–70 years of age with a Body Mass Index (BMI) of 20 to 29 kg/m2.
- Subjects with VAS score between 40 and 70 mm.
- Subjects with Knee osteoarthritis grade II to III of Kellgren and Lawrence assessed based on X-ray.
- Willing to refrain from use of glucosamine, chondroitin, MSM, DMSO, doxycycline, ibuprofen, aspirin or other NSAIDS (other than paracetamol as rescue medication) or any other pain reliever (OTC or prescription) during the entire trial.
- Female subjects of childbearing potential must be using a medically acceptable form of birth control. Female subjects of non-childbearing potential must be amenorrheic for at least 1 year or had a hysterectomy and/or bilateral oophorectomy.
- Results of screening are within normal range or considered not clinically significant by the Principal Investigator.
- Subjects ready to discontinue the use of supplementations including vitamins, glucosamine + chondroitin, herbals or other topical applications
- Agree to participate in the study through a written informed consent.
- Willing to comply with all the study related activities.

EXCLUSION CRITERIA

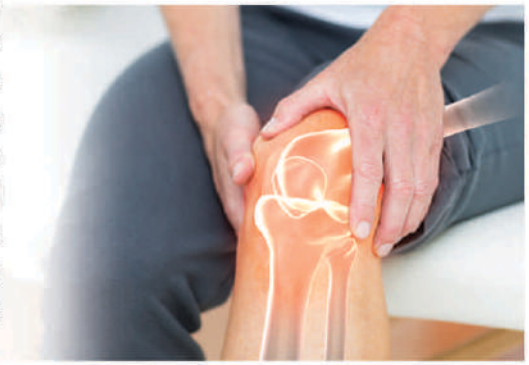
The exclusion criteria are as follows:

- Previous injury and or surgery to the knee.
- Expectation of surgery during the study period.
- Subjects with uncontrolled Diabetes (FPG>125 mg/dL) and Hypertension (Systolic > 120 mmHg and Diastolic >80 mmHg).
- Subjects suffering from COPD or having history of any respiratory or breathing disorders.

- Subjects used any immunosuppressive drugs in the last 6 months (including steroids or biologics) and those with history of immune system and autoimmune disorders.
- Female subjects, who are pregnant, breast feeding or planning to become pregnant during the study period.
- Subjects having known allergy to non-steroidal anti-inflammatory drugs (NSAIDs) (including aspirin) or has a suspected hypersensitivity, allergy or sensitivity to herbal products.
- Have taken any corticosteroid, indomethacin within 1 month prior to the enrollment or intra-articular treatment/injections with corticosteroid or hyaluronic acid within 6 months prior to enrollment.
- History of congestive heart failure or any vascular conditions.
- Subjects with HIV Positive status.

STATISTICAL ANALYSIS

The data generated in the clinical study will be analyzed by applying appropriate statistical method. Unless otherwise stated, all hypotheses will be tested at a significance level of 0.05 and 95% confidence interval. The Statistical analysis plan will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.



RESULTS

Demographics and baseline characteristics

Average age of subjects enrolled into the study was 52 years, approximately the same between both the groups at the time of screening. Total 16 males (53.3%) and 14 females (46.7%) participated in the study. Average BMI was 26.7 kg/m2, on the baseline visit.

Safety Results:

Vitals are monitored and recorded at all the visits. There was no clinically significant abnormality observed in test and control group subjects inferring the active product is safe for administration. The safety parameters including ECG and laboratory tests (CBC, RFT and LFT) were within normal limits on screening and on day 56.

Efficacy Results

Clinical features of Osteoarthritis including pain, stiffness and physical functions are assessed in this study by WOMAC and VAS scales.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a patient-reported outcome measure for the assessment of lower limb osteoarthritis. The WOMAC measure has been used for decades and is one of the most commonly used outcome measures in hip and knee osteoarthritis research. The WOMAC has been recommended as a trial endpoint by the Food and Drug Administration (FDA) and is noted as a potential measure for efficacy in recommendations for updates of FDA and European Medicines Agency (EMA) guidance and other working groups. In addition, the WOMAC has been recommended as one of the highest-performing outcome measures for knee and hip osteoarthritis, in terms of reliability, validity, responsiveness and interpretability. The WOMAC is often used as a comparator to assess the measurement properties of other outcome measures. The WOMAC is composed of 24 items over 3 subscales (5 for pain, 2 for stiffness and 17 for physical function). Participants rate their difficulty for each item.[5] WOMAC scale assesses Pain, Stiffness, and Physical function by three subscales WOMAC A, WOMAC B and WOMAC C.[6]

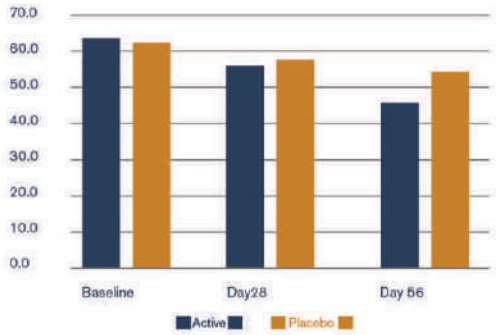
PARAMETER: WOMAC A (PAIN)

WOMAC A score in active group on baseline was 62.7 and 46.7 on day 56. WOMAC A score in placebo group on baseline was 61 and 54 on day 56. The improvement in WOMAC A score in Active group from baseline to day 56 is statistically highly significant. (P value 0.0001) compared to placebo group.

Parameter	Hypothesis Type	DF	Type III SS	Mean Square	F Value	Pr > F
WOMAC A (Pain)	3	1	395.047416	395.047416	21.03	0.0001

Visit	Statistics	Active	Placebo
Baseline	n	15	15
	Mean (SD)	62.7(6.23)	61.0(5.07)
	Median	65.0	60.0
	Min, Max	55,70	55,70
Day 28	n	14	13
	Mean (SD)	56.4(5.35)	58.1(3.84)
	Median	55.0	55.0
	Min, Max	50.65	55,65
Day 56	n	12	13
	Mean (SD)	46.7(5.37)	54.2(3.44)
	Median	45.0	55.0
	Min, Max	40.55	50,60

Graph for turmeric extract in joint
Health Graph for womac data (pain)



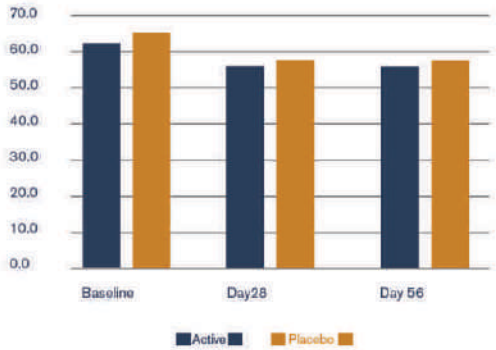
PARAMETER: WOMAC B (STIFFNESS)

WOMAC B score in active group on baseline was 63.3 and 54.2 on day 56. WOMAC B score in placebo group on baseline was 65.7 and 55.0 on day 56. There is improvement in WOMAC B score in Active group from baseline to day 56.

Parameter	Hypothesis Type	DF	Type III SS	Mean Square	F Value	Pr > F
WOMAC B (Stiffness)	3	1	7.700967	7.700967	0.61	0.4427

Visit	Statistics	Active	Placebo
Baseline	n	15	15
	Mean (SD)	63.3(3.09)	65.7(3.72)
	Median	65.0	65.0
	Min, Max	55,65	60,70
Day 28	n	14	13
	Mean (SD)	57.1(3.23)	59.6(4.77)
	Median	57.5	60.0
	Min, Max	50.60	55,65
Day 56	n	12	13
	Mean (SD)	54.2(4.69)	55.0(3.54)
	Median	55.0	55.0
	Min, Max	45,60	50,60

Graph for turmeric extract in joint
Health Graph for womac data (Stiffness)



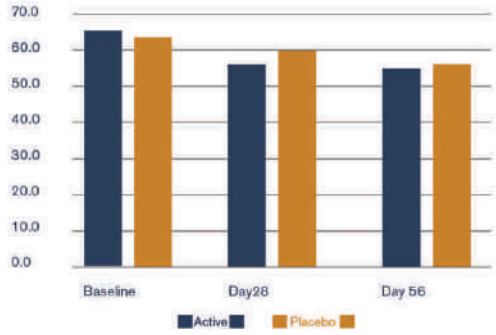
PARAMETER: WOMAC C (PHYSICAL FUNCTIONING)

WOMAC C score in active group on baseline was 65.0 and 54.6 on day 56. WOMAC C score in placebo group on baseline was 64.3 and 56.9 on day 56. There is improvement in WOMAC C score in Active group from baseline to day 56.

Parameter	Hypothesis Type	DF	Type III SS	Mean Square	F Value	Pr > F
WOMAC C (Physical functioning)	3	1	37.051172	37.051172	3.68	0.0681

Visit	Statistics	Active	Placebo
Baseline	n	15	15
	Mean (SD)	65.0(5.35)	64.3(3.72)
	Median	65.0	65.0
	Min, Max	55,70	60,70
Day 28	n	14	13
	Mean (SD)	57.9(3.78)	60.0(3.54)
	Median	60.0	60.0
	Min, Max	50,65	55,65
Day 56	n	12	13
	Mean (SD)	54.6(2.57)	56.9(3.84)
	Median	55.0	55.0
	Min, Max	50,60	50,65

Graph for turmeric extract in joint
Health Graph for womac data (Physical functioning)



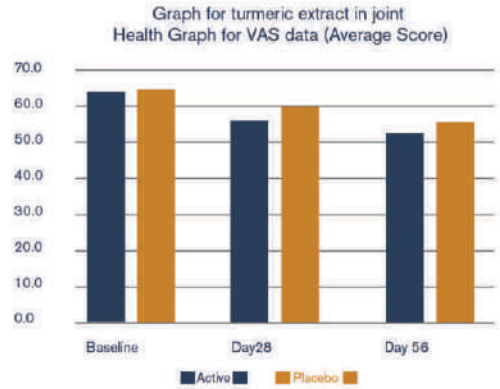
VAS

The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. Scores are based on self-reported measures of symptoms that are recorded with a single handwritten mark placed at one point along the length of a 10-cm line that represents a continuum between the two ends of the scale– "no pain" on the left end (0 cm) of the scale and the "worst pain" on the right end of the scale (10 cm). Measurements from the starting point (left end) of the scale to the patients' marks are recorded in centimeters and are interpreted as their pain. The values can be used to compare pain between patients with similar conditions from baseline to study end.[7]

VAS score in active group on baseline was 62.4 and 52.1 on day 56. VAS score in placebo group on baseline was 63.0 and 55.4 on day 56. The improvement in VAS score in Active group from baseline to day 56 is statistically highly significant. (P value 0.0001) compared to placebo group.

Parameter	Hypothesis Type	DF	Type III SS	Mean Square	F Value	Pr > F
Average of VAS (A - G)	3	1	49.58457392	49.58457392	22.24	0.0001

Visit	Statistics	Active	Placebo
Baseline	n Mean (SD) Median Min, Max	15 62.4(2.37) 61.4 59,66	15 63.0(1.46) 62.9 61,65
Day 28	n Mean (SD) Median Min, Max	14 57.9(2.02) 57.5 55,61	13 60.3(1.53) 59,3 59,63
Day 56	n Mean (SD) Median Min, Max	12 52.1(1.94) 52.1 49,55	13 55.4(1.61) 55,7 53,58



Pain is the predominant symptom of OA and is what usually leads those affected to seek medical care. The pain in OA is typically aggravated by joint use and relieved by rest. It tends to be localized to the affected joint (s) though may occur beyond and in some cases may be referred. In the early stages of disease, symptoms including pain are often intermittent becoming more frequent and severe as the disease progresses. Symptomatic osteoarthritis (OA) causes substantial physical and psychosocial disability. OA indirectly leads to worsening of co morbid conditions like diabetes, hypertension, cardiac illness and depression. It accounts also for substantial direct health-care costs related largely to the requirement for joint replacement surgery in those with end stage disease.[8]

CONCLUSION

Osteoarthritis is a chronic, inflammatory degenerative disease with pain, stiffness and restricted physical functions. Absocurcumin (Turmeric extract) has demonstrated an excellent safety and efficacy profile in osteoarthritis patients in present study. Absocurcumin (Turmeric extract) capsules when administered orally for a period of 56 days in osteoarthritis patients demonstrated significant improvement in clinical symptoms including pain, stiffness and physical functions as evidenced by both WOMAC and VAS scores. The patients starting responding to the treatment within a month of start of treatment. None of the patients had increase in the severity of symptoms and none of the patients discontinued the treatment. Treatment was well tolerated and there were no serious adverse effects related to study medication. Anti- inflammatory and antioxidant properties of turmeric extract proved to have favorable influence in lowering the disease progression on comparing with placebo group subjects. This clearly indicates that Absocurcumin (Turmeric extract) when administered orally has definitive role in the management of osteoarthritis patients.

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