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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLEDCLINICAL STUDY TO EVALUATE COMPARATIVE CLINICAL EFFICACY AND SAFETY OF BHC9619CP TURMERIC EXTRACT IN JOINT HEALTH

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ABSTRACT

Osteoarthritis (OA) is a chronic condition that impacts quality of life and functionality for which patients often seek dietary supplements to provide some relief. The purpose of this double-blind, placebo-controlled clinical trial was to assess the safety and efficacy of BHC9619CP Turmeric Extract on pain, stiffness, physical activity and general health and well-being in 30 adults with OA randomized into active intervention (n = 15) or placebo (n = 15) groups. Outcomes were assessed periodically for 56 days, including the Western Ontario McMaster Osteoarthritis Index (WOMAC), the Visual Analogue Scale (VAS) for pain, and safety. Normalized analysis (improvement over baseline) showed that significant alleviation of pain was observed in active intervention group. Results also revealed that the treatment improved the physical function of the patients by significantly reducing pain and improving stiffness as well as physical activity. The Product was also found to be safe in this study. In conclusion, daily consumption of BHC9619CP Turmeric Extract significantly alleviates pain and improvement in stiffness and physical activity over the treatment period of 56 days. BHC9619CP Turmeric Extract may offer a safe option for relief from symptoms and increased mobility for those with OA.

KEYWORDS: Curcuma longa; turmeric; joint health; efficacy; osteoarthritis; safety.

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disorder characterised by cartilage loss. It is extremely prevalent in society and is a major cause of disability. It is important to treat osteoarthritis effectively using a multidisciplinary approach tailored to the patient's needs (Hunter DJ, et al., 2014). 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 (Haq I, et al., 2003). The etiology of OA is multi-factorial and includes joint injury, obesity, aging, and heredity. OA ofthe 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. (Chen D, et al., 2017).

There is no standard for treatment and what is available is typically focused more on pain alleviation by a combination of pharmacological and nonpharmacological approaches rather than curative treatment. Even when pain alleviation protocols are prescribed, only half of the patients experience pain reduction (Messier SP, et al., 2004). The most commonly used medications include paracetamol 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 (Mora JC, et al., 2018). Some improvements may be achieved by weight-loss and physical activities, including physical therapy; however, this often does not lead to a full alleviation of symptoms (Karsdal MA, et al., 2014). Therefore, there is need to investigate alternative medicines as an optionfor symptomatic management.

Complementary and alternative medicine is being utilized for several years in various parts ofthe world to

alleviate symptoms of various Arthritic conditions. Complementary and alternative medicines used Turmeric extract since many years for treating osteoarthritis. Turmeric a rhizomatous herbaceous perennial plant (*Curcuma longa*) of the ginger family is a spice that has been used in culinary world since ages and received much interest from the medical/scientific worlds due to its potential analgesic, antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer properties (Kohli K, et al., 2005; Singh A, et al., 2017; Wang Z, et al., 2020). The main active component of Turmeric extract is Curcumin which has been known for its anti-inflammatory and antioxidant properties from ancient times and these properties are highly beneficial in management of Osteoarthritis (Shep D. Trials. 2019). Curcumin has been shown to block NF-κB activation increased by several different inflammatory stimuli. It suppressed inflammation through many different unknown mechanisms, thereby supporting its potential as an anti-inflammatory agent (Hewlings SJ, et al. 2017). The study by Madhu K, et al., 2013 was unique in using a turmeric extract that contained only polar substances, especially polysaccharides, and no curcumin. Turmeric and chondroitin sulphate both provided significant benefits by both PVAS and WOMAC score, with turmeric performing significantly better. However, combining turmeric and chondroitin provided no added benefit, which may be due to redundant effects as already suggested for curcumin and diclofenac. This study demonstrated potent anti-inflammatory and/or analgesic benefits for turmeric components other than curcumin (Madhu K, et al., 2013). Pre-clinical studies conducted on rats suggested that curcumin derived from turmeric extract is a gastro-protective agent and acts as a potent anti-ulcer compound, protecting against gastric mucosal injury (Mei X, et al., 2009; Sudjarwo SA, et al., 2005). A study has shown that curcumin acts as a potent anti-ulcer compound to protect indomethacin (NSAID)-induced gastric ulcer (Chattopadhyay I, et al., 2006).

A limited number of clinical studies were performed related to the efficacy and safety of turmeric extracts for OA and joint function, particularly for OA of the knee. These studies include several proprietary preparations from Turmeric extracts especially curcumin, with different diagnostic measurements, durations, controls, and blindness (Daily JW, et al., 2016; Hewlings SJ, et al., 2017; Kohli K, et al., 2005; Kuptniratsaikul V, et al., 2009; Madhu K, et al., 2013; Shep D, et al., 2019; Wang Z, et al., 2020).

Although all the above clinical studies have shown beneficial effects for OA of the knee,small number of patients enrolled, shorter study period employed in these studies and absenceof placebo control in some studies did not meet all rigorous clinical trial criteria to draw definitive conclusions on the usage of Turmeric extracts for the treatment of knee OA. Therefore, to further evaluate the product, this randomized, double-blind, placebo-controlled trial was undertaken, specifically in adults who were experiencing symptoms associated with OA of the knee to the extent that it was impacting quality of life, yet not severe enough to warrant prescription medication. The present study was designed to evaluate safety and efficacy of BHC9619CP Turmeric extract, as oral supplement in newly diagnosed or untreated patients with OA of the knee.

MATERIALS AND METHODS

Ethics

This was a randomized, double-blind, placebo-controlled clinical study conducted at a single research site located in Bangalore, Karnataka, India. The study was approved by the Shetty's Hospital Ethics Committee, Bangalore Karnataka, India on February, 04, 2020 and executed by Shetty's Hospital, Bengaluru, Karnataka, India. The study was conducted in accordance with the clinical research guidelines established by the Drugs and Cosmetics Act, 1940, of India; Drugs and Cosmetics Rules, 1945, of India; the International Conference on Harmonization recommended harmonized tripartite guideline regarding Good Clinical Practice; Part 56 of Title 21 of the Code of Federal Regulations (CFR), the Declaration of Helsinki, and ICMR-National Ethical Guidelines for Biomedical and Health Research.

Patient recruitment

Both male and female patients, between 40 and 70 years of age with Knee osteoarthritis gradeII to III of Kellgren and Lawrence and VAS score between 40 and 70 mm were screened based on typical history, clinical presentation, classical radiological findings, and fulfilling the classification for OA of the knees.

All participants who met the following inclusion criteria were selected for enrolment: (a) patients with a minimum pain Visual Analogue Scale (VAS) score between 40 and 70 mm;
(b) patient ambulant and requiring treatment with an anti-inflammatory drug and not satisfied with drugs being taken and seek a change; (c) patient willing to discontinue the use of supplementations including vitamins, glucosamine + chondroitin, herbals or other topical applications (d) patients willing to come for regular follow-up visits; and (e) participants had to be able to walk and give both verbal and written information regarding the study. Demographic data, physical examination, medical and medication history, comorbid conditions, and vital signs were recorded. All participants provided written informed consent. The exclusion criteria for the study included the following: (a) known hypersensitivity to herbal extracts or dietary supplements; (b) pregnant or lactating women and women of child bearing potential not following adequate contraceptive measure or women who were found positive for urine pregnancy test; (c) nondegenerative joint diseases or other joint degenerative diseases; (d) any previous injury and/or surgery to knee as well as surgical procedure is expected in recent future; (e)

current or recent (in the last 6 months) oral or intra-articular corticosteroid therapy; (f) history of congestive heart failure or any vascular conditions; (g) ongoing treatment with corticosteroids, indomethacin and hyaluronic acid; (h) patients with uncontrolled diabetes and hypertension (h) suffering from Chronic Obstructive Pulmonary Disease (COPD) or having history of any respiratory disorders; (i) patients with HIV positive status; (j) patients who needed high dose of NSAIDs or analgesics; and (k) inability to comply to study procedures.

Study design

The purpose of this trial was to assess the safety and efficacy of the study product BHC9619CP Turmeric extract on pain, stiffness, physical functioning based on WOMAC Score and VAS scale. Recruitment of patients for this trial commenced on February 18, 2020, and completed on August 24, 2020. In general, after undergoing phone- and in-person screening, and after signing an informed consent, 30 subjects were randomized in a 1:1 manner to either study interventional product or placebo group. Subjects were instructed to consume two 500 mg capsule either product or placebo twice daily after meals for a period of56 days and record in diary.

The subjects were advised to stop any use of over-the counter nonsteroidal anti-inflammatory drugs or pain relief products for at least 14 days before the randomization visit to permit an accurate baseline assessment of the WOMAC scale and its subscales. All enrolled subjects were instructed to avoid use of ibuprofen, aspirin or other NSAIDS (other than paracetamol as rescue medication) or any other pain reliever (OTC or prescription) during the entire trial.

Randomization and blinding

Both BHC9619CP Turmeric extract and placebo were soft gelatine capsules and were identical to allow for blinding. Both the products were packed identically in the same type of bottles. One bottle of capsules was dispensed at each study visit for once-daily dosing for 28 days. During the double-blinded treatment phase of the study, the subject and all personnel involved with the conduct of the interpretation of the study, including the investigators and investigational site personnel, were blinded to the medication codes. An authorized statistician, independent of the sponsoring organization, not involved in conduct or reporting of the study made random allocation cards using computer-generated random numbers. The randomization codes were recorded to avoid further confusion, and data were kept strictly confidential. The original random allocation sequences were accessible only to authorized persons on an emergency basis as per sponsor's standard operating procedures until the time of unblinding.

Intervention products

This study evaluated BHC9619CP Turmeric extract Capsules (Botanic Healthcare) and placebo (Maltodextrin). Both study product and placebo were manufactured by Botanic Healthcare. Subjects were dosed once daily for the study duration. Compliance was measured by questionnaire and the standard return pill-count method.

Intervention and compliance

All subjects were asked to take two 500 mg soft gel capsules (1000 mg) twice daily after meals (either BHC9619CP or placebo) per day. Subjects were provided with study visit plan. Study personnel conducted checks at scheduled visits to ensure compliance as per the protocol with special reference to medications and follow-up visits. A diary was provided to the patients to record their daily study and nonstudy medications and any adverse health event. Unused tablets were returned and were analysed for percent treatment compliance. All the 30 subjects completed the study.

Study assessments

All subjects were assessed at the baseline visit by the Western Ontario McMaster University Osteoarthritis Index (WOMAC), Visual Analogue scale (VAS) and wellbeing as physical examination, vital signs as well as concomitant medications. In addition, all subjects utilized a daily diary to record any use of rescue medication between study visits (rescue medicine, 500mg paracetamol to no greater than 2000 mg allowed). Subjects underwent repeat clinic visit testing on days 28 and 56 after the randomization visit.

The severity of knee OA based on a questionnaire, and physical examination before and after BHC9619CP treatment was assessed for the efficacy. The Western Ontario McMaster Index (WOMAC) was used for the assessment of pain, stiffness, and physical function in patients with OA of the knee to evaluate the efficacy of at Days 0, 28, and 56. The WOMAC questionnaire contains questions related to severity and frequency of symptoms such as swelling of the joint, grinding and clicking noises, knee catching or hanging up, the ability to straighten or bend knees, pain in the knees in different positions, knee functions, and the ability to perform daily functions. Other measures performed included determination ofphysician's and VAS pain scores.

Safety assessment

Safety was monitored throughout the course of the study by monitoring of blood pressure, ECG, liver function, kidney function, blood sugar, general immunity, and red blood cell activity (comprehensive metabolic panel, complete count with differential urinalysis); physical exam were considered for safety evaluations. The vitals and physical examination for safety were measured on Days 0, 28 and 56. Urine test for pregnancy was performed on female volunteers of child bearing potential. Adverse effects, if any, were recorded at each study visit.

Statistical analysis

All data are expressed as mean ± SD. Data were evaluated for statistical significance by t test or analysis of covariance depending on the number of comparisons made to reach the best possible statistical conclusion between patients receiving BHC9619CP and placebo. Results with $p < 0.05$ are considered statistically significant. Statistical Analysis Software (SAS) was used for data analysis.

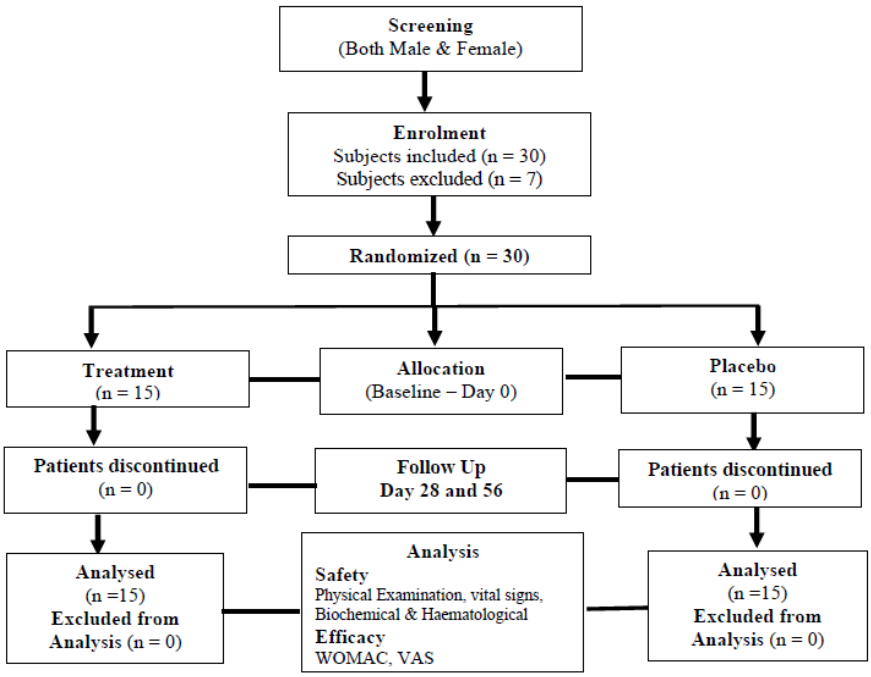

Figure 1: Study Design Flowchart of BHC9619CP turmeric extract.

RESULTS

Demographic characteristics of subjects

This study recruited from local advertisements in the community and screened 37 subjects to qualify and randomize 30 (2 cohorts of 15 subjects per group). 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/m^2, on the baseline visit.

Clinical efficacy

The data on the efficacy assessments, including WOMAC [i.e., WOMAC A (pain), WOMAC B (stiffness) and WOMAC C (physical function)] and VAS scores after 56 days of treatment, are presented in **Figure 2**. Detailed analyses pertinent to the overall WOMAC (A, B, C) scores and VAS scores are presented in **Table 1**. Analysis of covariance was applied to confirm the efficacy assessment. Mean scores were used for bilateral OA. The differences in the efficacy parameters between the baseline and after BHC9619CP treatment group compared with the placebo group were found to be significant ($p < 0.001$) for WOMAC A and VAS scores. However, no significant difference was observed between the baseline and the placebo group in these parameters.

Effect of BHC9619CP treatment on WOMAC score

The sub scores of WOMAC, namely, the three domains of pain, physical function, and stiffness, are provided in **Table 1**.

A comparative analysis of WOMAC A score (pain) at the baseline visit showed a mean valueof 62.7 ± 6.23 and 61.0 ± 5.07 for the treatment and placebo groups, respectively. However, a steady decrease in the WOMAC A score was observed at different time points in patientswith the BHC9619CP treatment, and a mean value of 46.7 ± 5.37 was observed on Day 56. The mean WOMAC A score for the placebo group was 54.2 ± 3.44 on Day 56. Overall, the BHC9619CP treatment group showed a statistically significant ($p < 0.001$) decrease in WOMAC A score indicating improvements in physical function by reducing pain (**Figure 2a and Table 1**).

The values of the sub scores of WOMAC are in agreement with the WOMAC overall score that BHC9619CP treatment significantly reduced the pain compared with placebo control andthere is improvement in stiffness and physical function when compared to baseline in patients with OA of the knee (**Figure 2a, 2b & 2c**).

Effect of BHC9619CP treatment on VAS pain scale

The VAS pain scale score was significantly reduced after BHC9619CP treatment. Briefly, on the baseline visit, a

mean score of 62.4 ± 2.37 and 63.0 ± 1.46 was reported by the active and placebo treatment groups of patients, respectively. On Day 56 (final visit), the pain score decreased significantly ($p < 0.001$) to 52.1 ± 1.94 in the active treatment group of patients with no statistically significant change, whereas it was 55.4 ± 1.61 in the placebo receiving patients. The study concluded that as per physicians' assessment, patients felt much better with BHC9619CP (active) when compared with placebo (**Figure 2d and Table 1**).

FIGURE 2 Bar graphs show the efficacy analyses with BHC9619CP Turmeric extract treatment. (a–d) The efficacy bar graphs are based on quality of life (QOL) questionnaire scores in patients with osteoarthritis (OA) of the knee (joint health) treated with BHC9619CP (Day 56) compared between placebo control and their baseline visit (Day 0). (a) BHC9619CP treatment shows a significant decrease in Western Ontario McMaster Index (WOMAC) A score indicating improvements in pain; (b) BHC9619CP treatment shows a significant decrease in WOMAC B score indicating improvements in stiffness; (c) BHC9619CP treatment shows a significant decrease in WOMAC C score indicating improvements in physical function; (d) reduction in the Visual Analogue Scale (VAS) pain scale score in the BHC9619CP group was conferred by Day 56.

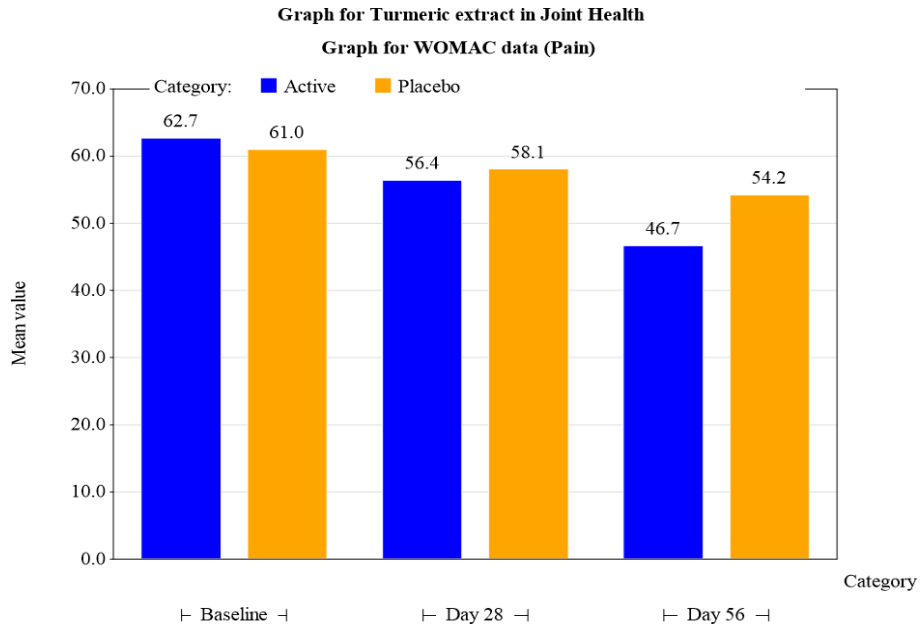

Figure 2a.

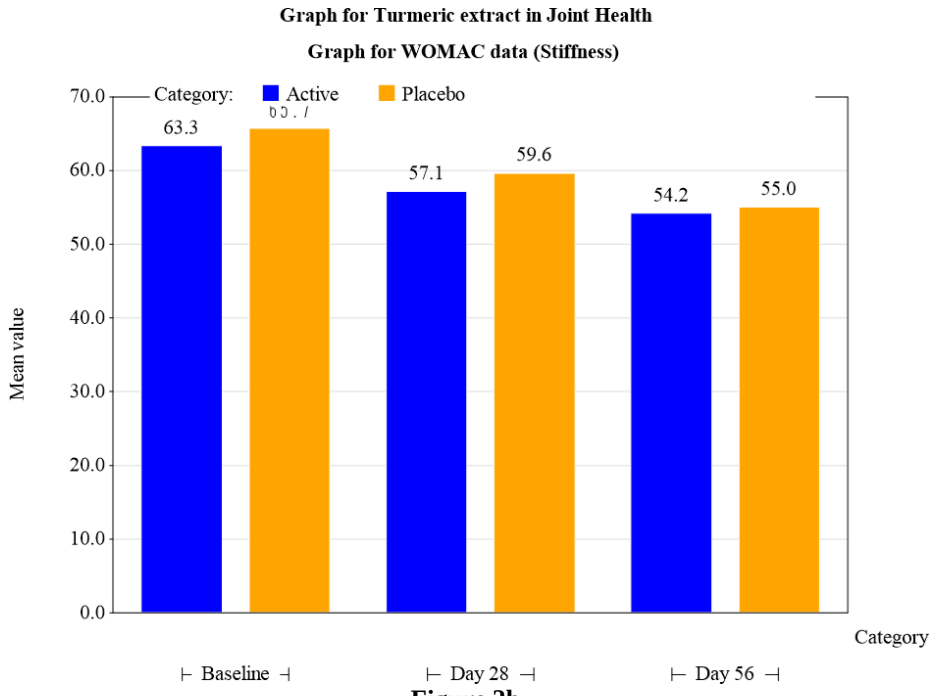

Figure 2b.

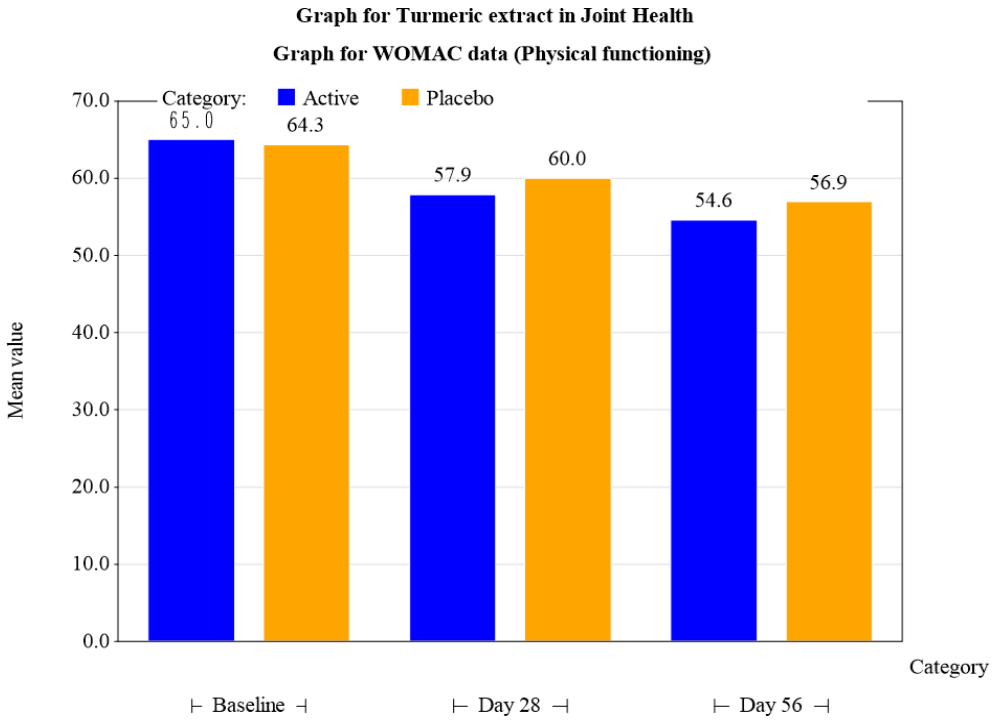

Figure 2c.

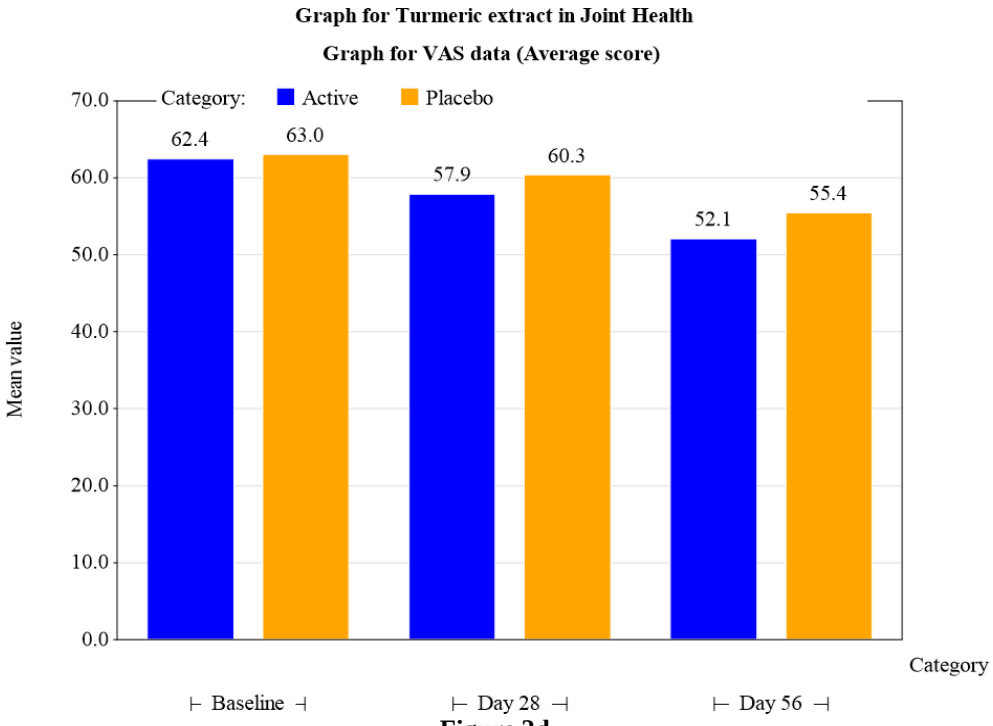

Figure 2d.

Safety evaluations and Adverse events

None of the enrolled subjects had abnormal medical history. No abnormality in physical findings was observed on the screening visit or during the study visits. The vital signs recorded in listings for physical examination did not show statistically significant changes that are recorded between the baseline and Day 56 of BHC9619CP or between the treatment groups. Systolic blood pressure and diastolic blood pressure pulse rate, respiratory rate, heart rate, and oral temperature were normal on the screening visits and during the study visits as well.

There were no statistically significant changes in the body weight and body mass index from baseline to the last visit or between the treatment groups. Vital signs, namely, blood pressure, respiratory rate, pulse rate, and any abnormal lab/diagnostic parameters recorded, were safe and thus support the safety of the agent BHC9619CP.

During the course of the study, 4 adverse events (3 subjects had nausea, 1 subject had headache) observed for four different subjects which were categorized as mild to moderate in severity with none of the events were judged to be related to study product in the Investigator's opinion. No clinically significant abnormal lab values were identified, and no statistically significant changes in the vitals were observed from the baseline to the final visits. Although few high values were reported, they were categorized as "not clinically significant" by the study investigator owing to their marginal borderline values from the lab reference ranges. The percentage of treatment compliance for 30 patients who completed the study was good. The events were resolved and closed, and the subjects completed all remaining study visits. No concomitant medications were allowed.

Table 1: Comparative analysis of 56-day efficacy measures with BHC9619CP versus placebo.

Parameter	BHC9619CP		Placebo		P value
	Baseline	Day 56	Baseline	Day 56	
WOMAC A score	62.7 ± 6.23	46.7 ± 5.37	61.0 ± 5.07	54.2 ± 3.44	**0.0001***
WOMAC B score	63.3 ± 3.09	54.2 ± 4.69	65.7 ± 3.72	55.0 ± 3.54	0.4427
WOMAC C score	65.0 ± 5.35	54.6 ± 2.57	64.3 ± 3.72	56.9 ± 3.84	0.0681
VAS pain scale score	62.4 ± 2.37	52.1 ± 1.94	63.0 ± 1.46	55.4 ± 1.61	**0.0001***

*** Statistically significant**

RESULTS AND DISCUSSION

This study demonstrated efficacy and safety of BHC9619CP Turmeric Extracts by alleviating pain and modulating physical activity in patients with knee osteoarthritis.

Use of herbal medicines and phytonutrients or nutraceuticals is gaining interest in therapies, including prevention and treatment of chronic diseases such as OA (Daily JW, et al., 2016).

In this context, Panahi Y, et al., 2014 have shown that curcuminoids significantly reduce WOMAC, VAS, and Lequesne's pain functional index scores and concluded that curcuminoids also represent an effective and safe alternative treatment for OA (Panahi Y, et al., 2014). Earlier in a study it was demonstrated that curcumin has a similar pain relief effect on patients with knee OA compared with diclofenac. Improvements in pain, stiffness, symptoms, functions of daily living, sports or recreational activities, and quality of life due tocurcumin have been attributed to its ability to inhibit COX-2, which results in the suppression of prostaglandin synthesis. Furthermore, curcumin has been shown to suppress several pro- inflammatory cytokines and mediators of their release, such as tumour necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), IL-8, and nitric oxide synthase (Shep D, et al., 2019). WOMAC scale assesses Pain, Stiffness, and Physical function by three subscales WOMAC A (pain), WOMAC B (stiffness) and WOMAC C (physical function) (Walker LC et al. 2018). The Visual Analogue Scale (VAS) is a validated, subjective measure for acute and chronic pain (Bendinger T, et al., 2016).

During the present study clinical features of Osteoarthritis including pain, stiffness and physical functions by using WOMAC score and VAS Pain scale scores were evaluated and it was observed that BHC9619CP Turmeric extract significantly improved these parameters when compared to placebo group. WOMAC A (Pain) score in active group was 62.7 ± 6.23 & 46.7 ± 5.37 on baseline and day 56, respectively. Whereas, in placebo WOMAC A score was 61.0 ± 5.07 & 54.2 ± 3.44 on baseline and day 56, respectively. The improvement in WOMAC A score in active interventional group from baseline to day 56 is statistically highly significant (P value 0.0001) and also higher pain reduction was observed in comparison to placebo. WOMAC B (Stiffness) score in active intervention group on baseline was 63.3 ± 3.09 and 54.2 ± 4.69 on day 56. WOMAC B score in placebo group on baseline was 65.7 ± 3.72 and 55.0 ± 3.54 on day 56. There was improvement in WOMAC B score in active intervention from baseline to day 56. Similarly, WOMAC C (Physical functioning) score in active intervention group on baseline was 65.0 ± 5.35 and 54.6 ± 2.57 on day 56. WOMAC Cscore in placebo group on baseline was 64.3 ± 3.72 and 56.9 ± 3.84 on day 56. There is improvement in WOMAC C score in active intervention from baseline to day 56.

VAS score was used to evaluate reduction in pain in active group and it was observed that theimprovement in VAS score in Active group from baseline to day 56 is statistically highly significant (P value 0.0001). The VAS score improvement in active intervention group was also higher in comparison to placebo group.

The therapy was well tolerated and all the participants completed the study duration. There were no significant adverse effects other than nausea and headache (minor to moderate category and unrelated as per investigators opinion) observed in the study. All the 30 subjects completed the study without any discontinuation and/or withdrawal.

Overall, both patients and physician's assessment demonstrated that BHC9619CP was better in reduction of knee osteoarthritic symptoms like pain, stiffness and physical activity in comparison to placebo.

The current study has a few limitations. This is a pilot study with a small group of subjects. However, studies with larger human cohort is required to confirm the conclusions of the present study. Use of a panel of inflammatory markers, including matrix metalloproteinase derived inflammation, a component of OA (Siebuhr A, et al., 2014), and interleukin 6, identified in the systemic circulation and synovial fluid of OA patients (Bonnet C et al., 2005), may provide distinctive effects of BHC9619CP on inflammation associated with OA. Despite some of these limitations, the present clinical trial demonstrated the safety and efficacy of BHC9619CP Turmeric Extract, in patients with OA of the knee.

SUMMARY AND CONCLUSION

The findings from the present study provide clinical evidence to support that biologically active component of BHC9619CP Turmeric extract specifically curcumin exerted analgesic/anti-inflammatory activity efficaciously in reducing joint pain and improving the physical functional ability. No serious adverse events were observed, thus supporting the pharmacological safety of BHC9619CP Turmeric extract to be considered as a viable candidate for the treatment of OA of the knee.

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