Avens Publishing Group
J Orthopedics Rheumatol
February 2023 Vol.:10, Issue:1

Clinical Validation of Incorporating Standardized Formula with Phytoconstituents in Knee Osteoarthritis: A Randomized, Placebo-Controlled Study

Keywords: Osteoarthritis; WOMAC; Boswellia; curcumin

Abstract

Background: Osteoarthritis (OA) is the most common joint disease with a prevalence of 22% to 39% in India and being foremost causes of nonfatal burden. The use of conventional medication can be associated with insufficient clinical management, serious side effects. The present research validates using Joint Support Product (JSP) a standardized, specially designed herbal extract-based formula with phytonutrients which are useful in the management of symptoms as well as regeneration in OA.

Method: Clinical trial was randomized placebo-controlled involving 150 patients with knee osteoarthritis included in two parallel groups equally. JSP and placebo were provided for 90 days. The celecoxib tablets up to 200 mg as rescue was allowed and recorded. The objectives of the study were to assess the effectiveness and safety of JSP in osteoarthritis by evaluating pain, stiffness, symptoms and anti-inflammatory activity to improve quality of life.

Results: Treatment of JSP in patients with osteoarthritis led to reduction in pain, stiffness and other related parameters to provide the symptomatic relief and thus improved quality of life. Treatment with JSP reduced the inflammatory markers by 50% suggestive potential joint restorative action. With JSP, most of the subjects showed reduced dependency on the analgesics as a rescue. There were no evident side effects of the JSP treatment.

Conclusion: It can be concluded from the study that JSP is safer and effective option in the management of OA. With treatment with JSP, most of the subjects showed reduced dependency on the analgesics as a rescue in the treatment tenure.

Open Access Research Article

Journal of Orthopedics & Rheumatology

Shridhar Pandya[1], Chetan Savaliya[2], Amol Gothwad[3], Tanuja Panchabhai[4], Gayatri Ganu[5] and Dheeraj Nagore[6]*

[1]*Director, Gplife Healthcare Pvt Ltd, 705-706, Orbit- 1 Building, Punagam-Saroli Rd, Near RRTM Market, Surat, 395010, India*

[2]*Director, Gplife Healthcare Pvt Ltd, 705-706, Orbit- 1 Building, Punagam-Saroli Rd, Near RRTM Market, Surat, 395010, India*

[3]*Consultant, Lokmanya Medical Research Centre Lokmanya Hospital, Floor 4, OPD 1, 314/B Telco Road, Chinchwad, Pune, 411033 Maharashtra, India*

[4]*Consultant, Atharv multispecialty Research center, Krishna chowk, Kirti Nagar, New Sanghavi, Pune 411027 Maharashtra, India.*

[5]*Director, Mprex Healthcare Pvt Ltd, 501, 514, Crossroads building, Bhumkar Chowk, Wakad, Pune 411057, India*

[6]*Director, Mprex Healthcare Pvt Ltd, 501, 514, Crossroads building, Bhumkar Chowk, Wakad, Pune 411057, India*

***Address for Correspondence**

Dr. Dheeraj Nagore, Mprex Healthcare Pvt Ltd, 501, Crossroads building, Bhumkar Chowk, Wakad, Pune 411057, India. Email: dheeraj@mprex.in

Submission: 19 October 2022
Accepted: 08 February 2023
Published: 13 February 2023

Introduction

Osteoarthritis (OA) is the common rheumatologic joint disease with a prevalence of 22% to 39% in India. OA was estimated to be one of the foremost causes of nonfatal burden [1]. It is a chronic progressively degenerating disorder with a collective etiology regarded by the loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis, and range of biochemical and morphological alterations of the synovial membrane and joint [2]. The pathophysiological alterations in chronic OA include softening, ulceration, focal disintegration of the articular cartilage along with synovial inflammation [3]. The clinical symptoms associated with OA are pain, with or without activity and weight-bearing; stiffness after inactivity leading to reduced range of the motion of the joints [4]. The common joints affecting includes knees, spine, shoulders and hips etc. OA of the knee is more prevalent as per the literature available [5].

The common pharmacological interventions include oral and topical analgesics, intra-articular corticosteroids, modified release dosage forms of the oral analgesics, hyaluronic acid, glutathione, chondroitin, vitamin, mineral and collagen supplementation etc along with non-pharmacological interventions like massage, exercise and weight loss etc [6].

Due to lack of self-healing capacity of the articular cartilage, OA is among the most challenging joint diseases and there is currently no cure for it [7]. The conventional OA medications are limited to control OA symptoms; moreover, none can reverse the damage in the OA joint. The newer medicines like biologically derived molecules and stem cell therapy and tissue engineering are in reassert phase and it is evident that these newer therapies provide uncertain clinical outcomes along with the side effects [8]. The use of conventional medication in OA management can be associated with often insufficient clinical management as well as serious side effects and high costs. However, phytotherapy have shown the potential for safe and effective management of arthritis [9].

Regenerative phytotherapy therapy holds the chance of repairing and regenerating damaged or lost tissues to restore the original structure and function. JSP is a standardized, specially designed herbal extract-based formula with phytonutrients in the management of symptoms as well as regeneration in OA and comprehensive trial with actual clinical outcomes will be very useful. The present clinical trial aims at generating evidences around safety and effectiveness of incorporating a phytoconstituents based product in the management of osteoarthritis.

ISSN: 2334-2846

Materials and Methods

Study objectives

The primary objectives of the study were to assess the effectiveness and safety of Joint Support Product (JSP) in subjects suffering from knee osteoarthritis based on changes in inflammatory market status like CRP, IL-6, performance of patient on pain VAS scale, local examination, clinical signs assessment of WOMAC from baseline to day 90 between groups. The secondary objectives of the study were to evaluate symptom improvement like morning stiffness, tenderness, tiredness and muscle spasms, along with improvement in quality-of-life score, reduction in dependency over analgesics from baseline to day 90 between groups. The tolerability and safety were also evaluated.

Inclusion criteria

Male and/or female volunteers aged between 40 to 80 years both inclusive were included. The subjects willing to follow the diet, exercise along with willing to come for regular follow-up visits were included. Based on the American College of Rheumatology (ACR) criteria, patients with osteoarthritis of the knee clinical OA of the knee is defined as knee pain and at least three out of six of the following criteria: age > 50 years, morning stiffness < 30 min, crepitus, bony tenderness, bony enlargement, and no palpable warmth.

Exclusion criteria

Patients with congenital arthropathy, rheumatoid arthritis, active gout, other type of arthritis with/without inflammation e.g. septic, fibromyalgia or collagen vascular disease were excluded. Patients with history of major trauma or surgery in the knee joint were not included in the study. The study excluded obese or diabetic patients, those with severe cardiac, renal, or hepatic disease, as well as pregnant or nursing women.

Methodology

Patients between 40-80 years (both inclusive) receiving standard treatment for knee osteoarthritis were screened for eligibility criteria. On screening visit, a written informed consent was obtained from subject for participation in the study. Subjects who were able to understand and agreed to comply with the planned study procedures and were available for all study visits.

Subject's demographic details were recorded. Subject underwent clinical examination. Blood samples of all eligible subjects were collected for biochemical and hematological investigations. Subjects were enrolled after meeting all inclusion criteria and not showing any exclusion criteria. On baseline visit (day 1), subject was recruited in the study and randomized to one of the two study groups as per the computer-generated randomization list either in JSP or in Placebo groups. Subjects were asked for occurrence of any adverse event during screening period. If subjects had any comorbidity or concurrent illness, the condition and medication was recorded. Subjects were screened for any other allergies for the ingredients of investigational product.

Subjects in both groups received education regarding diet and lifestyle. For 3 months, both groups consumed two tablets twice a day after meals, either JSP or placebo.

All the subjects were allowed to consume rescue medication as celecoxib tablet up to 200 mg in divided dosage as per requirement and to be terminated as soon as the symptoms subside. Subject were advised to continue concomitant medication other than protein supplements, antioxidant agents, vitamins, nutraceutical, Ayurvedic, herbal medication etc.

Drug compliance was assessed by the investigator on every follow up visit. If any subject continuously missed dosing for >3 consecutive days or total missed dose > 6 during the 30 days'period, subject was treated as drop out. Subjects were assessed for any adverse events during study period.

The subjects were asked to follow up on every month for 3 months i.e., day 30, 60 and 90. On each visit day, subject underwent clinical examination, symptoms, screening for any adverse event, assessment of pain and flexibility by VAS and WOMAC scoring. On baseline and day 90 visit all subjects were assessed for quality of life and changes in biochemical, inflammatory marker and hematological parameters.

Subjects were asked to contact investigator for adverse events between visits and provide details of rescue medication usage. After completion of 90 days, the subject was asked to stop the study medication. Investigator instructions were given for further treatment to the subjects.

Normality of the data was checked by "The Kolmogorov-Smirnov Test of Normality". Continuous variable i.e. age was summarized by overall using summary statistics i.e. the number of observations, mean and standard deviation with 95% CI (among normal distribution) analyzed by student t test and gender was analyzed using chi square test. In this study the changes in inflammatory marker status like CRP and IL-6, was analyzed using student t test and Mann Whitney U test. whereas, clinical signs assessment of WOMAC symptom, improvement like morning stiffness, tenderness, tiredness and muscle spasms, and quality-of-life score was analyzed by student t test. Pain on VAS scale, and change in pain, stiffness and physical difficulty domain score of WOMAC scale was analyzed by Mann Whitney U test. Reduction in dependency over analgesics is documented as number of events.

Intervention and dosage

The key ingredients in JSP are standardized and fortified extracts of Boswellia, Curcumin, Tinospora, Guggul, Nirgundi etc. Subjects from JSP and placebo group were respectively advised to take two tablets twice a day after meals for 90 days.

Sample size

Sample size calculation was performed by referring to the research done by Shep et. Al., 2019, [10] based on a power of 90% and a type I error rate of alpha of 0.05 (two-tailed), a sample size of 65 participants per group was required to detect an estimated difference of 1.24 in the mean pain scores between the treatment arms with a standard deviation of 2.5. A total sample size of 75 participants per treatment group was considered in this study.

Randomization

We intended to complete 150 subjects at the end of the study. We screened 156 subjects of which four were screen failure. Total

ISSN: 2334-2846

of 152 subjects entered the randomization out of which 150 subjects were considered for the final analysis (75 in each group). The patient disposition is depicted in Figure 1. This was a randomized study wherein all the subjects were randomly allocated (as per computer generated randomization list) to either one of the treatment arms i.e., JSP and placebo in 1:1 ratio. We received randomization schedule from qualified statistician, investigator enrolled the participants to respective study groups. The informed consent process is followed by instigator to obtain informed consent documents signed by patients.

Identical placebo in terms of color, size, shape, weight was followed in order to keep both investigator as well as the subject blind of which medication was being received. The de randomization process was kept in place in case of adverse event which needs to know about the treatment received by patient. The concealment of the investigational products was achieved by numbering the containers as per the subject's identity numbers and randomized accordingly. Statistical analysis has been done by using SPSS version 10.0.

Results

Demographic characteristics

There were 152 subjects enrolled into study and 150 subjects completed the study and data is analyzed (Figure 1). There were 75 evaluable subjects in each group. Both groups were comparable in their gender distribution and mean age. The details are presented in Table 1.

Changes in inflammatory markers between groups

In the present study, there was significant reduction (50%) in serum CRP levels in JSP treatment group compared to 23.55 % in placebo group (Figure 2). There was 48.84% reduction in IL-6 levels in JSP group compared to 14.75 % in placebo group (Table 2) (Figure 3).

Changes in pain score (VAS) between groups

The baseline pain score was comparable between groups. After treatment, there was significant (51.21% reduction) in VAS score in JSP group compared to 5.63 % in placebo group (Table 3) (Figure 4). In both the groups, the reduction in pain score was found to be statistically significant at P <0.05 from baseline to the end of the study.

Changes in WOMAC score between groups

The baseline WOMAC score of JSP and placebo groups were 66.73 and 62.24 respectively. After treatment, on day 90, there was significant (74.70%) reduction in WOMAC score in JSP group compared to 5.65% in placebo group (Figure 5).

We studied different domain scores of WOMAC scale such as pain, stiffness and physical difficulty scores. It was found that there was around 80% reduction in scores of all these domains compared to baseline in JSP group compared to around 10% reduction in placebo group. Compared between groups, JSP statistically reduced the pain, stiffness and physical difficulty in patients in 90 days treatment. In both the groups, the reduction in WOMAC score was found to be statistically significant at P <0.05 from baseline to the end of the study (Tables 4 & 5).

Changes in symptom between groups

It was observed in the present study that subjects were experiencing moderate to severe symptoms like morning stiffness, tiredness, tenderness and muscle spasms on baseline. After 90 days of treatment there were around 88%, 93.3%, 96% and 80%, respectively subjects from JSP group experienced no symptoms such as morning stiffness, tiredness, tenderness and muscle spasms. In both the groups, the improvement in all the above mentioned symptoms was found to be statistically significant at P <0.05 from baseline to the end of the study. These subjects were relieved of symptoms compared to around 10% subjects from placebo group (Figure 6).

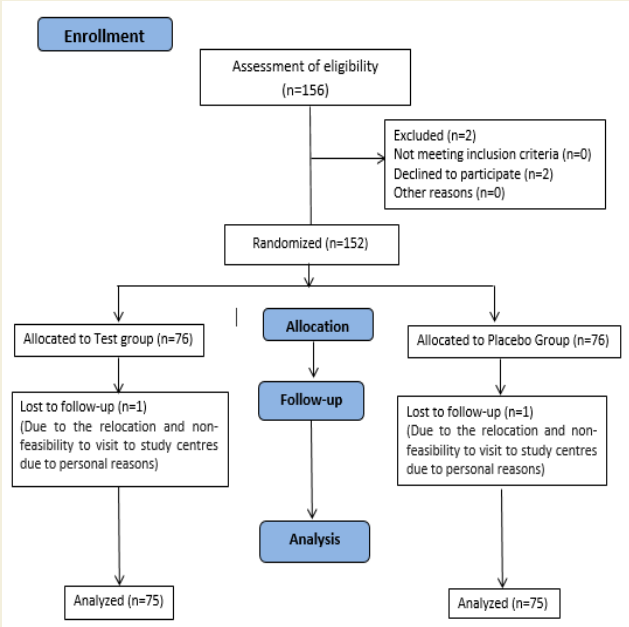

Figure 1: CONSORT diagram for the study.

ISSN: 2334-2846

Table 1: Demographic Details.

Groups	Treatment		Placebo	
Gender#	Male (n = 25)	Female (n = 50)	Male (n = 25)	Female (n = 50)
Age* (years)	52.73 ± 9.58		48.00 ± 6.20	

Data analyzed by *student t test, #Chi square test. Not significant p>0.05.

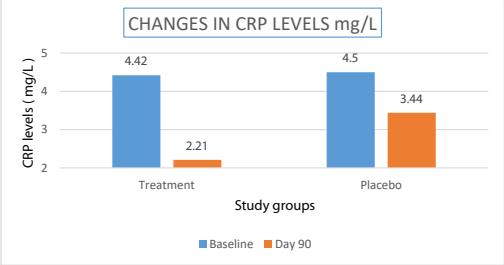

Figure 2: Changes in CRP levels.

Table 2: Changes in inflammatory markers.

CRP mg/L (Mean±SD			
Duration	Treatment	Placebo	P value
Baseline	4.42±2.66	4.50±2.85	0.865
Day 90	2.21±1.49	3.44±3.02	
Mean difference	2.21±1.37)*	1.06±0.69	<0.00001
% Reduction	50%	23.55%	
IL-6 pg/mL (Mean±SD)			
Duration	Treatment	Placebo	P value
Baseline	5.61±3.82	6.10±3.61	0.051
Day 90	2.87±1.35	5.20±3.78	
Mean difference	2.73±3.41#	0.89±0.53	0.01242
% Reduction	48.84%	14.75%	

*Data analyzed by student t test, # analyzed by Mann Whitney U test. Significant at p<0.05.

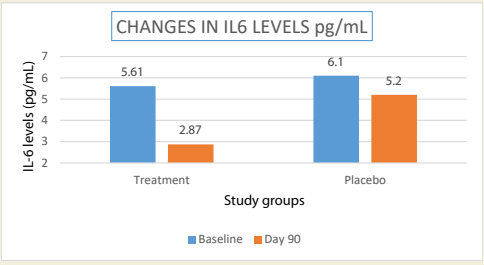

Figure 3: Changes in IL-6 levels.

Table 3: Changes in pain score (VAS).

VAS Scores			
Duration	**Treatment**	**Placebo**	**P value**
Baseline	7.79±0.76	7.81±0.82	0.836
Day 30	5.89±0.81	7.13±0.93	
Day 60	5.27± 0.87	7.51±0.52	
Day 90	3.80±0.77	7.37±0.49	
Mean difference(baseline-day 30)	1.89±0.31#	0.70±0.57	< 0.00001
Mean difference(baseline-day 60)	2.52±0.55#	0.30±0.67	< 0.00001
Mean difference(baseline-day 90)	3.99±0.65#	0.44±0.76	< 0.00001
% Reduction	51.21%	5.63%	

#analyzed by Mann Whitney U test. Significant at p<0.05.

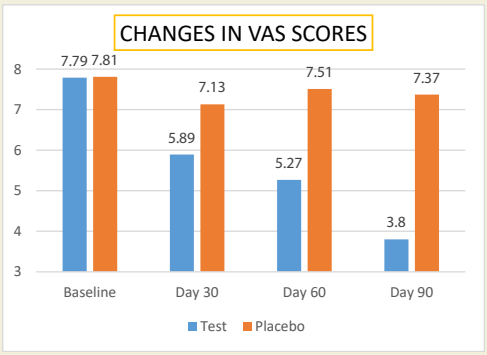

Figure 4: Changes in VAS scores.

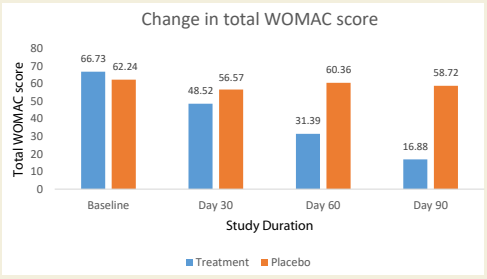

Figure 5: Changes in Total WOMAC score between groups.

Table 4: Changes in Total WOMAC score between groups.

Total WOMAC Scores			
Duration	**Treatment**	**Placebo**	**P value**
Baseline	66.73±4.63*	62.24±3.42	< 0.00001
Day 30	48.52±4.23	56.57±2.68	
Day 60	31.39±2.98	60.36±3.32	
Day 90	16.88±2.75$	58.72±4.13$	< 0.00001
Mean difference(baseline-day 30)	18.21±3.30*	5.67±1.65	< 0.00001
Mean difference(baseline-day 60)	35.35±3.44*	1.88±4.71	< 0.00001
Mean difference(baseline-day 90)	49.89±4.73*	3.52±5.24	< 0.00001
% Reduction	74.70%	5.65%	

*Data analyzed by independent student t test;$Data analyzed bydependent student t test. Significant at p<0.05.

Changes in lipid profile between groups

Subjects with high cholesterol levels at baseline, showed significant reduction in the total cholesterol and LDL cholesterol after treatment of JSP after 90 days. There were no significant post treatment changes in the lipid profile of subjects with normal lipid levels at baseline in both groups (Table 6).

Changes in biochemical and hematological parameters

There were no clinically significant changes in hematological and biochemical parameters like liver function and kidney function test post treatment.

Changes in Quality-of-life score between groups

The average baseline QoL (Quality-of-life) Score was 34.07 in both the groups. It was reduced to 12.37±3.23 in JSP group and 33.48 ±3.20 in placebo group after 90 days of treatment. There is significant

ISSN: 2334-2846

Table 5: Changes in pain, stiffness and physical difficulty domain score of WOMAC scale.

Pain Score (Mean±SD)			
Duration	Treatment	Placebo	P value
Baseline	13.24±2.78	13.15±1.74	0.548
Day 90	2.92±1.51	11.75±1.40	
Mean difference	10.32±2.87#	1.40±2.06	<0.001
% Reduction	77.94%	10.64%	
Stiffness Score (Mean±SD)			
Duration	Treatment	Placebo	P value
Baseline	5.20±1.14	5.21±1.06	0.833
Day 90	1.05±0.85	4.59±0.89	
Mean difference	4.15±1.18#	0.63±1.16	<0.001
% Reduction	79.80%	11.90%	
Difficulty Score (Mean±SD)			
Duration	Treatment	Placebo	P value
Baseline	48.29±3.80	43.88±2.76	<0.001
Day 90	12.91±1.75	39.80±3.49	
Mean difference	35.39±4.04#	4.08±4.32	<0.001
% Reduction	73.26%	9.29%	

#Analyzed by Mann Whitney U test. Significant at p<0.05.

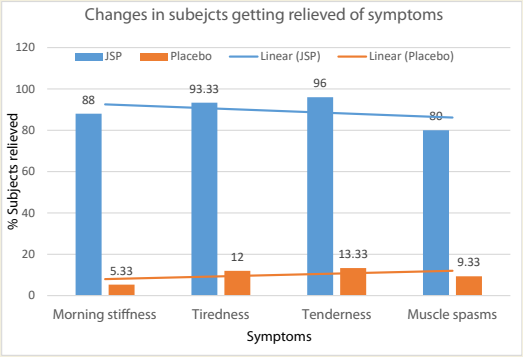

Figure 6: Changes in subjects getting relieved of symptoms between groups.

Table 6: Changes in elevated cholesterol levels between groups.

Parameter Mg/dl	Test		% Reduction	Placebo		% Reduction
	Baseline	Day 90		Baseline	Day 90	
Cholesterol	215.26± 13.08	187.39± 10.54*	12.94	226.09± 14.50	223.53± 14.62	1.13
Triglycerides	158.02± 44.68	136.63± 36.41*	13.53	131.14± 49.92	132.61± 51.24	1.12
HDL	45.09± 9.86	42.40 7.32	5.96	54.88± 11.81	55.33± 13.41	0.81
VLDL	31.60± 8.94	27.33 7.28*	13.51	26.23± 9.98	26.52 10.25	1.10
LDL	138.57± 13.30	117.67± 12.22*	15.08	144.98± 14.48	141.68± 14.24	2.27

*Data analyzed by student t test. Significant at p<0.05.

Table 7: Changes in Quality-of-life score.

QoL Score (Mean±SD)			
Duration	**Treatment**	**Placebo**	**P value**
Baseline	32.47±5.56	35.67±4.81	0.2000
Day 90	12.37±3.23$	33.48±3.20$	
Mean difference	20.09±5.95*	2.19±4.11	<0.001

*Data analyzed by independent student t test; $Data analyzed by dependent student t test. Significant at p<0.05

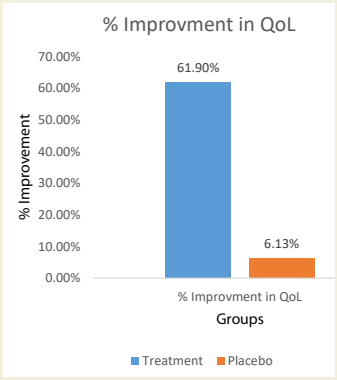

Figure 7: Improvement in quality of life score between groups.

improvement in quality of life of subjects in JSP treated group compared to placebo evident by reduced QoL (Quality-of-life) Score (Table 7) (Figure 7).

Changes in dependency on rescue analgesic medication between groups

We proposed percent responder subjects between groups as a measure to depict the reduced dependency over analgesics in both groups. The responder subject was defined as subjects showing 50% or more reduction in number of events in which the rescue of analgesic medicines was used. This comparison was with the baseline events of the analgesic consumption reported by subjects. After 90 days treatment with JSP there were 92% responders to the treatment compared to 8% in placebo group. There were statistically more subjects showing reduction in the dependency on analgesic medication in JSP than placebo.

There were fifteen adverse events recorded (7 events from JSP group and 8 events from placebo group). The mild adverse events like nausea, hyperacidity, headache, wound cut were resolved completely in 2-3 days. There was no need of rescue medication for the adverse events needed.

Discussion

OA is characterized by deterioration of joint cartilage, change in underlying bone, and synovitis. OA has a slow onset i.e. usually begin in the later age of life (age ≥ 40 yrs.). OA has a prevalence rate of 22 % to 39 % in India. Established literature shows high prevalence of OA in women as compared to men. OA of the knee is a major cause of mobility impairment, particularly among females. OA not only leads to discomfort to the patients but it also affects the quality of life. There are various rescue medications prescribed to patients such as oral and topical analgesics, intra-articular corticosteroids, modified release dosage forms of the oral analgesics, hyaluronic acid, glutathione, chondroitin, vitamin, mineral and collagen supplementation etc. along with non-pharmacological interventions like massage, exercise and weight loss etc. Conventional OA medications cannot reverse the damage caused to the OA joints due to lack of self-healing capacity of articular cartilage. Conventional OA medications can cause serious side effects and high costs. However, phytotherapy is safe and effective for managing arthritis.

ISSN: 2334-2846

The Joint Support Product (JSP) is a novel formulation containing the mixture of standardized and fortified extracts of *Boswellia, Curcumin, Tinospora, Guggul, Nirgundi* etc. The present randomized controlled trial was designed to evaluate the efficacy and safety of JSP versus Placebo for the short-term treatment (90 days) of symptomatic osteoarthritis of the knee. Parameters like inflammatory markers (CRP and IL-6), pain score(VAS), WOMAC scores, change in symptoms, lipid profile changes, biochemical and hematological parameters quality of life and dependency on rescue medication were studied.

Boswellic acids inhibit the synthesis of the pro-inflammatory enzyme 5-lipoxygenase (5-LO), and in vitro studies show that they can reduce pain and inflammation. In contrast to non-steroidal antiinflammatory drugs (NSAIDS), which accelerates articular damage in arthritic conditions, boswellic acids have been shown to significantly reduce glycosaminoglycan degradation. [11,12] Curcumin can reduce inflammation by decreasing the production of interleukin-1 and IL-6 [13]. The 3-acetyl-11-keto-β-boswellic acid (AKBA) is the most potent inhibitor of 5-lipoxygenase. The T. cordifolia extract (TCE) and the compounds isolated from T. cordifolia have been shown to possess immunomodulatory, anti-proliferative, and anti-angiogenic effects in various in vitro models. The anti-inflammatory effects of eugenol were attributed to its effect to prevent neutrophil/macrophage chemotaxis and prostaglandin synthesis as well as cyclooxygenase II enzyme expressions. Moreover, eugenol dimers exhibited a chemo preventive effect by inhibiting the cytokines expression in macrophages [14-16]. It was also revealed that eucalyptol acts by inhibiting a known sensor of noxious cold, called the human transient receptor potential cation channel, belonging to subfamily A, member 1 (TRPA1). Other studies, on the other hand, have concluded that it may involve a non-opioid mechanism. Inhalation of eucalyptus oil was effective in decreasing the pain and blood pressure following total knee replacement surgery [17]. It has been proposed that V. negundo leaf oil is a potent anti-inflammatory agent that works by inhibiting COX-2 without interfering with COX-1 pathways [18]. Constituents of the Piper species have shown in vitro inhibitory activity against the 5-lipoxygenase and COX-1 enzymes responsible for leukotriene and prostaglandin biosynthesis [19].

An increase in C-reactive protein levels indicates systemic inflammation. Researchers have suggested earlier that CRP itself might contribute to OA. Metabolic syndrome and obesity are risk factors for OA and increase CRP levels. Hence, reducing CRP levels could reduce inflammation and slow degenerative joint changes [20]. Pro-inflammatory mediators like IL-6 promote disease progression. The incidence and severity of OA were associated with elevated levels of IL-6. By inducing matrix-degrading enzymes, IL-6 contributes to cartilage pathology [21]. After 90 days treatment of JSP there was significant reduction (50%) in serum CRP levels whereas the placebo group shows reduction of only 23.55%. There was 48.84% reduction in IL-6 levels in JSP group compared to 14.75% in placebo group. Thus, indicating a promising effect in reducing inflammation caused by OA.

The effectiveness of the JSP can be attributed to the phyto-constituents used in the formulation. Evidence suggests that *Boswellia* reduces inflammation, prevents cartilage damage, and controls disease progression [22]. It has been revealed that *Boswellia* significantly reduced pain and stiffness in patients of OA. Boswellic acid promotes extracellular matrix formation in joints and chondrocyte production for cartilage repair [23]. Boswellic acid treatment has potential role of downregulating pro-inflammatory cytokines such as TNF, IL-1, IL-2, IL-4, IL-6, and IFN involved in joint degenerative changes [24].

Guggul's anti-inflammatory and antiarthritic properties are well proven fact, Z-guggulsterone are associated with inhibition of GFAP expression, as well as the proinflammatory cytokines IL-1, IL-6, and TNF in osteoarthritis [25].

In one study, Tinospora treatment restored bone health by reducing proinflammatory mediators such as TNF and interleukin-1, shifting the balance of mediators of bone remodeling toward anti osteoclastic activity [26].

VAS scores are based on self-reported measures of pain on 0-10 scale where zero represents “no pain” and ten as the “worst pain”. It provides the basis of ranking the pain severity from patient perception [27]. Many studies depicted role of curcumin in management of osteoarthritis similar in efficacy to nonsteroidal anti-inflammatory drugs, and glucosamine but with much more safety. [28] The phytonutrients from *Vitex negundo* are proven to ameliorate nociception and inflammation by inducing peripheral and central analgesic activity [29]. These are the important constituent’s in JSP. Thus after treatment, there was significant (51.21% reduction) in VAS score in JSP group compared to 5.63% in placebo group. Thus, indicating beneficiary effect in pain management in OA.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is widely used clinically validated in the evaluation of Hip and Knee Osteoarthritis. It is a self-administered questionnaire consisting of 24 items divided into 3 subscales: pain (five questions), stiffness (two questions), and physical function (17 questions) [30]. Higher scores represent worse pain, stiffness, and functional limitations. As OA interferes in daily activities through pain and stiffness of joints its very valuable that treatment with JSP not only lowers the total WOMAC score (74.70%) but individually all three subsets are statistically reduced up to 80% after the treatment. Apart from this after 90 days treatment of JSP, the patient’s experienced no symptoms such as morning stiffness, tiredness, tenderness and muscle spasms by around 88%, 93.3%, 96% and 80% respectively. This gives the symptomatic relief and that can be contributed to overall improvement in joint function and thus the improved quality of life perception of the patients. This is also justified by the significant improvement in quality of life of subjects in JSP treated group compared to placebo evident by QoL (Quality-of-life) Score.

JSP has also shown an additional lipid lowering effect in subjects having high baseline cholesterol levels but no significant effects were observed in the lipid profile of subjects with normal cholesterol levels at baseline in both groups.

Patients with OA often use rescue medications like analgesics for the pain management but these drugs can potentially cause various side effects like liver damage, nausea, dizziness, developing addiction and tolerance, etc. after chronic use. After 90 days treatment with JSP the subjects showed 50 % decrease in incidence of dependency on rescue analgesics. Thus, indicating beneficial effect in pain management during OA.

ISSN: 2334-2846

By virtue of the composition of the phytoconstituents in JSP, it offered wholesome effectiveness in the management of OA including analgesic, anti-inflammatory, regenerative activities with no adverse events related to the JSP. Thus administration of JSP to OA patients will reduce their dependency on the analgesics with symptomatic relief as well as will work on the root cause of degenerative processes at joints by providing chondroprotective action.

Treatment of JSP in patients with osteoarthritis led to reduction in pain, stiffness and other related parameters to provide the symptomatic relief and thus improved quality of life. Treatment with JSP could reduce the inflammatory markers by 50% which can have potential joint restorative action. After treatment with JSP, most of the subjects showed reduced dependency on the analgesics as a rescue in the treatment tenure. There were no evident side effects of the JSP treatment. JSP has potential to provide symptomatic relief but also helps in repair and restoration of degenerating joints in osteoarthritic patients.

Acknowledgments

The authors would like to acknowledge the research team and the back-office team involved in the research work. We would like to acknowledge the support from all study site staff, investigators and back-office team.

Declaration of conflict of interests and funding

Dr. Shridhar Pandya and Dr. Chetan Savaliya are directors in GPlife Healthcare Pvt. Ltd. Other authors declare non competing interests. Authors received funding from GPlife Healthcare Pvt. Ltd.

Compliance with Ethics Guidelines

We conducted a randomized placebo-controlled trial involving patients suffering from osteoarthritis of knee recruited from the outpatient department of Lokmanya Medical Research Centre, Lokmanya Hospital, Chinchwad, Pune; Atharva Multispecialty Research Centre, New Sanghvi, Pune. The study was approved by Institutional Ethics Committee, Lokmanya Medical Research Centre, and was registered with the Clinical Trial Registry of India (CTRI/2022/01/039179).

References

1. Pal CP, Singh P, Chaturvedi S, Pruthi KK, Vij A (2016) Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop 50: 518-522.
2. Dieppe P (2022) Epidemiology of the Rheumatic Diseases Second Edition. AJ Silman, MC Hochberg (eds). Oxford: Oxford University Press. 31: 1079-1080.
3. Symmons D, Mathers C, Pfleger B (2002) Global Burden of Osteoarthritis in year 2000: Global burden of disease 2000 study. World health report. 2002: 5.
4. Akinpelu AO, Alonge TO, Adekanla BA, Odole AC (2009) Prevalence and pattern of symptomatic knee osteoarthritis in Nigeria: A community-based study. Internet J Allied Health Sci Pract 7: 3.
5. Felson DT (1988) Epidemiology of hip and knee osteoarthritis. Epidemiol Rev: 10:1-28.
6. Mora JC, Przkora R, Cruz-Almeida Y (2018) Knee osteoarthritis: pathophysiology and current treatment modalities. J Pain Res: 11:2189-2196.
7. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, et.al. (2007) OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 15: 981–1000.
8. Zhang W, Ouyang H, Dass CR, Xu, J (2016) Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone research 4: 15040.
9. Lindler BN, Long KE, Taylor NA, Lei W (2020) Use of Herbal Medications for Treatment of Osteoarthritis and Rheumatoid Arthritis. Medicines 7: 67.
10. Shep D, Khanwelkar C, Gade P, Karad S (2019) Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. Trials 20: 214.
11. Siddiqui MZ (2011) Boswellia serrata, a potential antiinflammatory agent: an overview. Indian J Pharm Sci 73: 255-261.
12. Barbara J. Fougère, CHAPTER 19 - Approaches in Veterinary Herbal Medicine Prescribing, Editor(s): Susan G. Wynn, Barbara J. Fougère, Veterinary Herbal Medicine, Mosby, 2007, Pages 275-290, ISBN
13. Akuri MC, Barbalho SM, Val RM, Guiguer EL (2017) Reflections about Osteoarthritis and Curcuma longa. Pharmacogn Rev 11: 8-12.
14. Ragavi R, Saritha A Surendran (2018) Commiphora mukul: An Overview. Research J Pharm and Tech 11 : 3205-3208.
15. Raja AF, Ali F, Khan IA, Shawl AS, Arora DS (2011) Acetyl-11-keto-β-boswellic acid (AKBA); targeting oral cavity pathogens. BMC Res Notes 13:406.
16. Sannegowda KM, Venkatesha SH, Moudgil KD (2015) Tinospora cordifolia inhibits autoimmune arthritis by regulating key immune mediators of inflammation and bone damage. Int J of Immunopathol Pharmacol 28: 521-531.
17. Batiha GE, Alkazmi LM, Wasef LG, Beshbishy AM, Nadwa EH, et al. (2020) Syzygium aromaticum L. (Myrtaceae): Traditional Uses, Bioactive Chemical Constituents, Pharmacological and Toxicological Activities. Biomolecules 30: 202.
18. Nikhil Chandorkar, Srushti Tambe, Purnima Amin, Chandu Madankar (2021) A systematic and comprehensive review on current understanding of the pharmacological actions, molecular mechanisms, and clinical implications of the genus Eucalyptus, Phytomedicine Plus 1: 100089
19. Chattopadhyay P, Hazarika S, Dhiman S, Upadhyay A, Pandey A, Karmakar S, Singh L (2012) Vitex negundo inhibits cyclooxygenase-2 inflammatory cytokine-mediated inflammation on carrageenan-induced rat hind paw edema. Pharmacognosy Res 4:134-137.
20. Kozijn AE, Tartjiono MT, Ravipati S, van der Ham F, Barrett DA, et.al. (2019) Human C-reactive protein aggravates osteoarthritis development in mice on a high-fat diet. Osteoarthritis Cartilage 27:118-128.
21. Wiegertjes R, Van de Loo FAJ, Blaney Davidson EN (2020) A roadmap to target interleukin-6 in osteoarthritis. Rheumatology 59: 2681-2694.
22. Vishal AA, Mishra A, Raychaudhuri SP (2011) A double blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. Int j med sci 8: 615-622.
23. Bi D, Chen G, Cheng J, Wen J, Pei N, Zeng H, Li Y (2020) Boswellic acid captivated hydroxyapatite carboxymethyl cellulose composites for the enhancement of chondrocytes in cartilage repair. Arabian Journal of Chemistry 13: 5605-5613.
24. Bairwa K, Jachak SM (2016) Nanoparticle Formulation of 11-Keto-β-Boswellic Acid (KBA): Anti-inflammatory Activity and In Vivo Pharmacokinetics. Pharm Biol 54: 2909-2916.
25. Dang SJ, Wei WB, Li RL, Song CX, Xu J (2022) Z-Guggulsterone Relieves Neuropathic Pain by Inhibiting the Expression of Astrocytes and Proinflammatory Cytokines in the Spinal Dorsal Horn. Journal of Pain Research 15: 1315.
26. Sannegowda KM, Venkatesha SH, Moudgil KD (2015) Tinospora cordifolia inhibits autoimmune arthritis by regulating key immune mediators of inflammation and bone damage. Int j immunopathol pharmacol 28: 521–531.

ISSN: 2334-2846

27. Alexander I (2007) Electronic medical records for the orthopaedic practice. Clin orthop relat res 457: 114–119.

28. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragulpoontawee M, Lukkanapichonchut P (2014) Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Clin Interv Aging 9: 451–458.

29. Maniyar YA, Sriraj D (2017) Peripheral and central analgesic activity evaluation of ethanolic extract of Vitex Negundo flowers in experimental animals. International Journal of Basic & Clinical Pharmacology. 6. 2701.

30. Hmamouchi I, Allali F, Tahiri L, Khazzani H, Mansouri LE, Ali Ou Alla S, et. al. (2012) Clinically important improvement in the WOMAC and predictor factors for response to non-specific non-steroidal anti-inflammatory drugs in osteoarthritic patients: a prospective study. BMC Res Notes 5: 58.