International Journal of Research and Review
DOI: https://doi.org/10.52403/ijrr.20210401
Vol.8; Issue: 4; April 2021
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Randomized, Placebo Controlled Clinical Trial to Evaluate the Efficacy and Safety of HFPM-01 in Improving Pain, Stiffness, and Inflammation in Patients Suffering from Knee Osteoarthritis

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ABSTRACT

Objective: Osteoarthritis is a common chronic joint condition which causes stiffness and difficulty in moving, loss of muscle tone, strength and stamina. All these difficulties affect daily activities and quality of life and may also have an impact of mental health. Globally over 9.6% men and 18.0% women aged over 60 years has symptomatic osteoarthritis worldwide. It is the second most common rheumatologic problem and it is the most frequent joint disease with a prevalence of 22% to 39% in India. Considering the increasing prevalence and limitations of the conventional treatment for the management of Osteoarthritis, the current research aims at systematic clinical validation of the HFPM-01 in subjects primarily suffering from knee osteoarthritis.

Materials and Methods: 90 subjects were enrolled in the study and were randomized to one of the three treatment groups. Subjects were undergoing clinical examination. Vitals were recorded. Blood samples were collected for readings of CRP. Subjective questionnaire scores evaluation was performed like SF-36 health survey score, VAS scale, WOMAC questionnaire. Changes in symptoms severity were noted like morning stiffness, tiredness, tenderness, and muscle spasms along with assessment of GI symptoms.

Results: The change in WOMAC score, the increase in SF-36 score, the decrease in VAS score, the decrease in CRP levels, and the reduction in GI symptoms were found to be 33%, 308%, 60.44%, 52%, 40% respectively. Swelling, inflammation and pain was reduced from moderated to mild and eventually to no symptoms.

Conclusion: This explains that HFPM-01 tablet is significantly effective in improving SF36 score WOMAC and VAS scale score. It is effective in reducing pain, swelling, and stiffness of knee joints, also improves the mobility of knee joints, and provides gastro protection being effective in managing pain and stiffness. HFPM-01tablet is safe and effective in the management of Osteoarthritis.

Key words: Osteoarthritis, WOMAC, VAS, CRP, Gastro protective

INTRODUCTION

Osteoarthritis is a common and disabling condition that represents a substantial and increasing health burden with notable implications for the individuals affected, health-care systems, and wider socioeconomic costs [1]. The prevalence of the population associated with aging and increasing obesity along with a growing number of joint injuries is becoming more common, with worldwide estimates suggesting that 250 million people are currently affected [2]. Osteoarthritis (OA) is the most common type of arthritis in both developed and developing countries. It is a

chronic, progressive musculoskeletal disorder characterized by gradual loss of cartilage in joints which results in bones rubbing together and creating stiffness, pain, and impaired movement. The disease most commonly affects the joints in the knees, hips, hands, feet, and spine. The disease is associated with modifiable and non-modifiable risk factors such as obesity, lack of exercise, genetic predisposition, bone density, occupational injury, trauma, and gender [3]. Osteoarthritis can be categorized into two groups primary and secondary. Primary osteoarthritis is a chronic degenerative disease and is related to aging while secondary arthritis usually occurs due to secondary factors such as injury, diabetes, and obesity [4]. According to World Health Organization (WHO), 9.6% of men and 18.0% of women aged over 60 years has symptomatic osteoarthritis worldwide. Osteoarthritis is the most common rheumatologic problem and it is the most frequent joint disease with a prevalence of 22% to 39% in India. Pharmacological interventions include non-opioid analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), topical analgesics, opioid analgesics, and intra-articular steroid injection [5]. Additional complementary interventions employed for OA include the use of physiotherapy and antidepressant therapies, patient education, and weight control [6]. These treatments may prove ineffective in some patients and often have serious adverse effects [7]. Gastrointestinal complications are frequently reported with NSAIDs. The conventional medications possess limitation of providing symptomatic relief for transient period not acting on the deeper reasons of inflammation, oxidative stress and degenerative metabolic changes. Overall quality of life of subjects becomes compromised though on the analgesic medication. Hence there seems to be a requirement for drugs with good efficacy with overall improvement in quality of life of subjects suffering from OA. Specifically, there is a need for safe and effective drugs for patients who do not respond well to conventional medical therapy. Such patients are turning increasingly to natural product medicines [8].

With understanding the limitations of the conventional treatment for the management of OA, and Phytoconstituents known to play a major role in the management of arthritis, Siddhayu Ayurvedic Research Fdn. Pvt. Ltd. has come up with a polyherbal formulation conceptualized to be safe and effective in the management of the osteoarthritis. The product under the selection of composition holds the potential to be effective in not only managing pain and inflammation but also trying to treat the root cause and improve the quality of life of subjects with osteoarthritis. This research aims at systematic clinical validation of the same in subjects primarily suffering from knee osteoarthritis.

MATERIAL AND METHODS

Materials

HFPM-01 Formulation was used for the study as an investigational product. It consists of *Boswellia serrata, Zingiber officinale, Withania somnifera, Curcuma longa, Pluchea lanceolata* as key ingredients out of total 9 ingredients. The dose of HFPM-01 was 1 tablet thrice a day after meals with water for 90 days.

Methods

After getting approval from the ethics committee, the study was registered on the CTRI website. The CTRI registration number is CTRI/2020/07/026655. Patients were enrolled in the study only after registration of study on the CTRI website. The subjects were recruited after screening for compatibility with inclusion and exclusion criteria. Total 90 subjects were recruited and were grouped as 30 subjects in each group. Group 1 was served with HFPM-01, in prescribed dosage group 2 was control group received only analgesics as and when required and group 3 was

treated with Glucosamine 500 mg thrice daily.

The primary objectives of the study were to evaluate the safety and efficacy of HFPM-01 by assessing changes in performance of patient on pain VAS and the WOMAC scale, to monitor the improvement in SF-36 health survey score. We evaluated degree symptomatic relief including pain, inflammation, stiffness, swelling, joint flexibility, weight-bearing capacity, levels of inflammatory mediator like CRP in blood. We determined the proportion of subjects requiring analgesics as rescue medication, gastrointestinal symptoms due to treatment, like stomach pain, heartburn, vomiting, nausea, constipation/ diarrhea, etc.

The secondary objectives of the study were to evaluate tolerability of study drug by tracking adverse events, serious adverse events during the study period, pain status, and improvement in symptoms for other than knee pain if any (Shoulder, backache and muscle spasms).

Inclusion Criteria

Patients of either sex, 40 to 70 years of age and diagnosed with OA of knees fulfilling the ACR classification criteria were included in the study. The patients having minimum pain VAS score > 8 on walking in one or both knees during the 24 hours preceding recruitment were considered to be included in the study. The patients may or may not receiving regular anti-inflammatory or analgesic drugs or ones who were not satisfied with drugs being taken and seek a change were included in the study. Patients who were willing to come for regular follow up visits and agreeing to give written informed consent were considered.

Exclusion Criteria

Patients with congenital arthropathy, rheumatoid arthritis, active gout, other types of arthritis with/without inflammation were excluded from the study. Patients with a known history of coagulopathies, osteoarthritis of any other joint except knee and ones with a history of major trauma or surgery in the knee joint were exempted from the study. Patients with uncontrolled diabetes and hypertension were not considered. Patients with Body mass index (BMI) >40 kg/m2 and with any severe cardiac, renal, and hepatic disease were excluded. Vulnerable population and patients who had participated in any clinical trial within 30 days before enrollment were not considered for the study. Patients that found unfit from the view point of investigator were excluded from the study.

Study procedure

After the ethics committee's approval, the clinical study was registered on the CTRI website. Male and female subjects of age between 40 to 60 years (both inclusive) attending the study site(s) were screened for eligibility criteria. On the screening visit, written informed consent was obtained from subjects for their participation in the study. Subjects were undergoing clinical examination Subject's vitals were recorded. The subject was considered for further evaluation as per the inclusion and exclusion criteria. Subjects were called the next day morning on empty stomach for laboratory testing. The subject's blood samples were collected for laboratory testing. On baseline visit, the subject was recruited in the study if he or she meets all the inclusion criteria. As per the computer-generated randomization, subjects were randomized in one of the three groups. Clinical examination and the subject's vitals were recorded. All the subjective questionnaire scores were filled like SF-36 Health Survey score, VAS scale, WOMAC questionnaire. At baseline visit and every follow-up visit. Subjects were advised to consume the given product in a prescribed dosage. Subjects were advised to continue her/ his concomitant medication other than antioxidant agents, weight loss management, vitamins, anti-inflammatory drugs, hormones, nutraceuticals, Ayurveda, Siddha, Unani, herbal /homeopathic

medicines, etc. The record of concomitant medication was kept in the CRF. The NSAID agents were not allowed in the test and glucosamine treatment group except as a rescue medication for pain. The record of the same was also documented in CRF. Drug compliance was assessed by the investigator on every follow-up visit. Subjects who continuously missed dosing for >3 consecutive days or total missed dose > 9 during the study period were treated as dropouts. Subjects were called to respective study sites for follow-up visits after every month up to 3 months after the baseline visit. On every follow-up visit, Subjects were undergoing clinical examination. The subject's vitals were recorded. All the subjective questionnaire scores and symptom gradation were recorded in CRF. Subjects were critically examined for adverse events. All details were recorded in the CRF along with the rescue medication if present. On the third follow-up visit (i.e., Day 90) following activities were done Subject was undergoing clinical examination. The subject's vitals were recorded. Blood samples were collected for readings. All the subjective questionnaire scores were filled like SF-36 health survey score, VAS scale, WOMAC questionnaire. Subjects were scored on their symptoms like morning stiffness, tiredness, tenderness, and muscle spasms. Subjects were asked about GI symptoms. After completion of 3 months of study treatment, all the subjects were asked to stop trial medications and take the advice of the investigator for further treatment. All the subjects were closely monitored for any adverse event starting from baseline visit till the end of the study visit.

STATISTICS

Sample size consideration

Sample size calculation is derived taking considerations of primary and secondary outcomes by a qualified statistician. The software used for the calculation of sample size is SPSS version 10.0

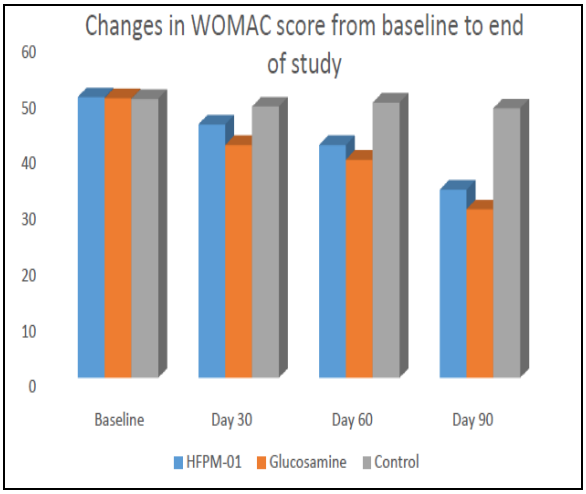
RESULTS

DEMOGRAPHIC DETAILS

In the present study, 115 subjects were screened. 10 subjects were screened for failure as per the decision of the investigator as were having to present uncontrolled diabetes. Out of 105 subjects, 15 lost to follow up in the study. 90 subjects were considered evaluable cases at the end of the study. Out of 90 completed subjects, the mean age of HFPM-01 group subjects was 48.5 ± 5.75 years and the mean age of glucosamine and control group subjects were 49.2 ± 6.06 and 46.7 ± 5.3 years respectively. There were an equal number of male and female subjects i.e., 15 males and 15 females in each group.

CHANGES IN WOMAC SCORE

In HFPM-01 group % change in the WOMAC score from day 0 to day 90 was 33 % and in the glucosamine group percent change was 39 %. On the other hand, control group represented a very less % change in the WOMAC score of 3.4 %. When compared between groups the HFPM-01 group and glucosamine group represent a comparable reduction in WOMAC score from day 0 to day 90 as compared to the control group. The results are shown in **Graph 1.**

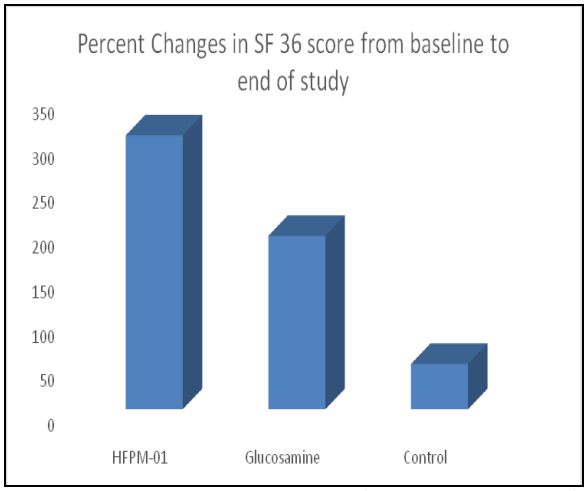


Graph No. 1: Changes in WOMAC score from baseline to end of the study

CHANGES IN SF 36 SCORE

In HFPM-01 group represent an increase in % change in SF-36 score from

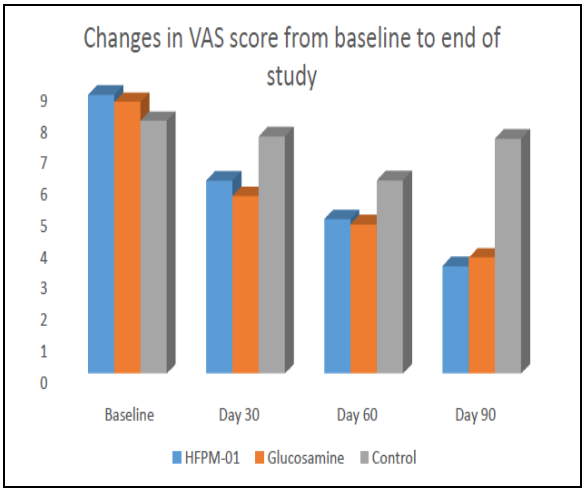
day 0 to day 90 was 308 % and in the glucosamine group % change was 195 %. On the other hand, control group represented 51 %. When compared between groups the HFPM-01 group presented significant increase in SF 36 score compared to the glucosamine group as well as the control group. The results are depicted in **Graph 2.**



Graph No. 2: Changes in SF 36 score from baseline to end of the study

CHANGES IN VAS SCORE

HFPM-01 and glucosamine treatment represented a decrease in VAS score from baseline to end of the study. The % decrease was 60.44% and 58.43% in HFPM-01 and glucosamine treatment group respectively whereas in the control group the % decrease was around 7%. There was a significant change in VAS score by HFPM-01 and glucosamine treatment when compared with the control group. The results are depicted in **Graph 3.**



Graph No.3: Changes in VAS score from baseline to end of the study

CHANGES IN CRP LEVEL

There were increased CRP levels in all three groups on the baseline. There was a decrease in CRP levels after treatment of HFPM-01 and Glucosamine. The percent decrease observed in HFPM-01 and Glucosamine treated groups were 52 and 36% respectively. The control group didn't decrease the CRP levels from baseline to end of the study. The results are depicted in Table no. 4.

Table no.4: Changes in CRP level in Glucosamine, HFPM-01 treated and control groups from baseline to end of the study:

Groups	Change in CRP level (mg/L) Mean ± SD			
	Baseline	Day 90	% Change	P-Value
HFPM-01	5.15 ± 6.68	2.47 ± 1.80	52	0.0193
Control	5.46 ± 5.61	5.39 ± 4.42	1.3	0.8270
Glucosamine	5.12 ± 3.86	3.26 ± 2.76	36	0.0001
P-Value control vs. HFPM-01	0.8422	0.032		
P-Value Glucosamine vs. HFPM-01	0.9855	0.1953		

Between-group analysis by one-way ANOVA test, within-group analysis by paired t-test, Significant at P≤0.05

CHANGES IN SEVERITY OF SYMPTOMS

Changes in frequency of subjects experiencing heartburn

In the present study the HFPM-01 test group 12 subjects suffering from GI symptoms like heartburn on the baseline which reduced by 66.7 % from baseline to day 90. In the glucosamine treatment group 14 subjects presenting heartburn symptoms on the baseline which reduced by 21.4 % from baseline to day 90. In the control treatment group 13 subjects presenting heartburn symptoms on the baseline which reduced by 7.7 % from baseline to day 90. HFPM-01 treatment has the potential to

provide relief from GI-related symptoms like heartburn in comparison to the glucosamine and control treatment group.

Changes in frequency of subjects experiencing constipation

In HFPM-01 test group 10 subjects suffering from GI symptoms like constipation on the baseline which reduced by 40 % from baseline to day 90. In the glucosamine treatment group 13 subjects suffering from constipation on the baseline which was reduced by 23.1 % from baseline to day 90. In the control treatment group 12 subjects presenting constipation symptoms on the baseline which reduced by 8.3 % from baseline to day 90. HFPM-01 treatment has the potential to provide relief from GI-related symptoms like constipation in comparison to the glucosamine and control treatment group.

Changes in frequency of subjects according to severity score for morning stiffness

On baseline 56.7 and 43.35 subjects from HFPM-01 treatment group reported moderate to severe morning stiffness which was comparable to 63.3 and 36.6 in glucosamine treated group. In the control group 50% of subjects reported moderate and the rest 50% reported severe morning stiffness. On day 90, similar proportion of subjects from the control group were representing moderate and severe morning stiffness. In the glucosamine and HFPM-01 treatment group, there was a gradual shift in subjects representing morning stiffness from moderate to mild and eventually no symptoms. There were 10 subjects from HFPM-01 treatment group who reported no morning stiffness and around 3% in the glucosamine treatment group reported no morning symptoms. It is evident from results that both glucosamine and HFPM-01 treatment group showed effectiveness in relieving morning stiffness of patients but HFPM-01 showed better activity than glucosamine.

Changes in frequency of subjects according to severity score for tiredness

On the baseline, 70% and 30% of subjects from the HFPM-01 treatment group reported moderate to severe tiredness which was comparable to 66.6 and 33.3% in the glucosamine treated group. In the control group 33% of subjects reported moderate and the rest 66% reported severe tiredness. On day 90 similar proportion of subjects from the control group were representing moderate and severe tiredness. In the glucosamine and HFPM-01 treatment group, there was a gradual shift in subjects representing tiredness from moderate to mild and eventually no symptoms. There were 4 subjects from HFPM-01 treatment group who reported no tiredness and no subject in the glucosamine treatment group reported no tiredness.

It is evident from results that both glucosamine and HFPM-01 treatment group showed effectiveness in relieving tiredness of patients but HFPM-01 showed better activity than glucosamine.

Changes in frequency of subjects according to severity score for Muscle spasms

On baseline subjects from HFPM-01, glucosamine and control treatment group reported moderate to severe muscle spasms which were comparable. On day 90 similar proportion of subjects from the control group were representing moderate and severe muscle spasms indicating no relief. In the glucosamine and HFPM-01 treatment group, there was a gradual shift in subjects representing muscle spasms from moderate to mild and eventually no symptoms. There were 10 subjects from HFPM-01 treatment group who reported no muscle spasms and around 5 in the glucosamine treatment group reported no muscle spasms. It is evident from results that both glucosamine and HFPM-01 treatment group showed effectiveness in relieving muscle spasms of patients but HFPM-01 showed better activity than glucosamine.

Changes in frequency of subjects according to severity score for Inflammation and Swelling

On baseline subjects from HFPM-01, glucosamine and control treatment group reported moderate to severe inflammation and swelling which was comparable. On day 90 similar proportion of subjects from the control group were representing moderate and severe inflammation and swelling indicating no relief. In the glucosamine and HFPM-01 treatment group, there was a gradual shift in subjects representing inflammation and swelling from moderate to mild and eventually no symptoms. It is evident from results that both glucosamine and HFPM-01 treatment group showed effectiveness in relieving inflammation and swelling of patients equally or comparably.

Changes in frequency of subjects according to severity score for joint flexibility

On baseline subjects from HFPM-01, glucosamine and control treatment group reported moderate to severe difficulty in joint flexibility which was comparable. On day 90 similar proportion of subjects from the control group were representing moderate and severe difficulties in joint flexibility indicating no relief. In the glucosamine and HFPM-01 treatment group, there was a gradual shift in subjects representing difficulty in joint flexibility from moderate to mild and eventually no symptoms. There were 8 subjects from HFPM-01 treatment group who reported no difficulty in joint flexibility and around 3 in the glucosamine treatment group reported no difficulty in joint flexibility. It is evident from results that both glucosamine and HFPM-01 treatment group showed effectiveness in relieving difficulty in joint flexibility of patients but HFPM-01 showed better activity than glucosamine.

Changes in frequency of subjects according to severity score for weight-bearing capacity

The weight-bearing capacity of subjects was significantly improved in the glucosamine and HFPM-01 treatment group compared to the control group.

DISCUSSION

Osteoarthritis condition is involving mediators of intra- and extracellular pro-inflammatory cytokines, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), e.g., nuclear factor Kappa-B (NF-kB), pro-inflammatory enzyme cyclooxygenase-2 (COX-2). The inflammatory activity precipitates in development of pain and related to function disability which can be evaluated by using The Western Ontario and McMaster Universities Arthritis Index (WOMAC) which is commonly used outcome measure for osteoarthritis. It is a validated and widely used instrument for assessing parameters like knee and hip pain, stiffness and physical function. [9]

WOMAC combined score is the sum of the pain sub score, stiffness sub score and physical function sub score assessed on WOMAC Index. [10]

Treatment with HFPM-01 significantly reduced the WOMAC score from baseline to end of the study. Curcumin, Boswellia serrata, Bioperine and Ginger from HFPM-01 formulation may have contributed in improvement in joint flexibility and reduction in pain evident by WOMAC score. These herbs are proven anti-inflammatory in action. Curcumin, ginger is preventing collagen degradation and inhibition of pro-inflammatory mediators such as prostaglandins, COX, nitric oxide and NF-kB and down-regulation of the pro-inflammatory cascade evident by many researches already published. [11]

CRP is activator in promotion of pro-inflammatory cytokines, which increases the inflammatory response. There are many studies represents the connection between elevated CRP levels in OA which is was significantly associated with pain and decreased physical function. [12,13]

In this study CRP is evaluated as inflammatory marker which may act as

contributing factor in disease progression in patients with OA. [13] In the present study, there were increased CRP levels in all three groups on baseline. There was significant decrease in CRP levels after treatment of HFPM-01. Decrease in CRP levels in patients belong to HFPM-01 treatment group shown possible mechanism Z. officinale extract as an anti-inflammatory activity by reducing serum level of TNF-α and high-sensitivity C-reactive protein (hs-CRP). [14]

Quality of life of recruited subjects was assessed using SF-36 questionnaire along with general health and energy status. SF-36 Health Survey (SF-36) scale scores also describe the health burden of arthritis and to be responsive to clinical indicators of arthritis severity. [15] These parameters altogether were considered to reflect the overall quality of life of the individual suffering from OA.

From present study it was evident that the control group did not improve quality of life but HFPM-01 improved QoL score by three folds compared to baseline.

Shallaki (Boswellia serrata) mainly have its activity on lipoxygenase pathway. Combination of Sunth (Zingiber officinale), and Shallaki (Boswellia serrata) possess potent analgesic activity. Thus, the observed significant improvement in QoL, is due to reduction of pain. [16]

Assessment of pain intensity is one of the primary outcomes used to determine the progression of OA. It is highly clinically relevant and relatively easy to measure. VAS is a reliable, valid, responsive, and frequently used pain outcome measure. The visual analog scale (VAS) is a pain rating scale the visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. [17]

HFPM-01 treatment represented a decrease in VAS score from baseline to end of the study. The analgesic activity to HFPM-01 could be the contribution of Withania somnifera, Boswellia serrata, Zingiber officinale, and Curcuma longa due to anti-inflammatory and chondro-protective activity confirmed through other clinical trials as well. Nirgundi from HFPM-01 possess pain-suppressing activities, possibly mediated via inhibition of prostaglandin synthesis. The possible role of anti-oxidant activity of W. somnifera on its anti-inflammatory properties has been already reported. Many experimental results have shown that W. somnifera improved VAS score by improving pain response, antioxidant status and general wellbeing [18,19]

Drug therapies like non-opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) in management of OA can develop gastrointestinal complications. HFPM-01 possesses such ingredients which are gastro protective in nature and hence evaluated for its effectiveness in this several number drugs related GI complication present in patients with OA.

The present data represent that herbs like turmeric, chopchini extract (Bark) and ginger used in HFPM-01 formulation have its promising effect on GI related complications like nausea, hyperacidity, heartburn and constipation etc. [20] The absence of gastric disturbance and improved compliance and quality of life can contribute to the better prognosis of the results in chronic OA patients.

Symptoms such as pain, stiffness, tenderness in joints, fatigue or tiredness due to join pain are some of the symptoms set that defines the quality of life of subjects. Pain and stiffness in the morning, after sitting, or after prolonged rest are most common. First aim of the treatment to OA should focus on the symptom alleviation so patients can experience ease while mobilizing. [21,22]

In the present study HFPM-01 treatment group experienced shift of subjects experiencing symptoms such as morning stiffness, tiredness, muscle cramps, tenderness to mild to no symptoms. This result can indicate that HFPM-01 possess the potential to provide relief from the symptoms related to OA.

It was evident from the study that the onset of relief from pain and stiffness was within 7 days from consumption of HFPM-01 as per patient diary.

Inflammation in OA is chronic and low-grade inflammation, involving mainly innate immune mechanisms. In OA, the synovial fluid has been found to contain multiple inflammatory mediators including plasma proteins like C-reactive protein, prostaglandins (PGE2), leukotriene's (LKB4), cytokines, nitric oxide etc. This expression can induce matrix metalloproteinase and other hydrolytic enzymes (including cyclooxygenase two and prostaglandin E) resulting in cartilage breakdown secondary to collagen destruction. [23]

Swelling can be a result of osteophyte formation, or due to an effusion caused by synovial fluid accumulation. Swelling contribute to disabilities in OA, mainly related to pain, difficulty in walking, climbing stairs, performing household chores, and sitting upright and have a negative psychological impact, all of which can lead to a decreased quality of life. [24]

In the present study subjects experiencing inflammation and swelling were gradually decreased in HFPM-01 treatment group which indicates that HFPM-01 not only reduce pain perception but may be acting to reduce inflammation and swelling resulting in more sustained action. Further the gastro protective activity demonstrated by HFPM-01 can allow its usage for long period of time.

In patients with OA, the reduction in muscle strength is attributed to myofibril atrophy, reduction of muscle quality and defective muscle regeneration along with the bony deformity at synovial joint contribute to the joint rigidity. [25]

In the present study HFPM-01 treatment has improved the joint flexibility which can further improve range of motion and thus can improve the physical activities in patients with OA.

Knee kinetics plays an important role in range of motion to knee joint. The healthy cartilage adapts morphology and mechanical features so as to respond to loading and weight bearing as well. [26] In the present study, treatment of HFPM-01 has improved weight bearing capacity of patients with OA that can in turn improve physical activities and thus quality of life.

There were no adverse events related to study products.

CONCLUSION

It can be concluded from data that there is anti-inflammatory, analgesic activity exhibited by HFPM-01 treatment in patients with OA. There was quicker symptom relief and was sustained for period of time. There was improved quality of life of subjects with gastro protective activity offered by HFPM-01. The treatment with HFPM-01 proved to be safe and effective for long term use in subjects with OA. HFPM-01 can be used as a Monotherapy in mild pain and stiffness in osteoarthritic conditions while can be used as an adjuvant when there is necessity to use analgesics as rescue.

Acknowledgments: The authors would like to acknowledge all the personnel that contributed to the activities of the research

Funding Statement: The financial support to conduct this study was given by Siddhayu Ayurvedic Research Fdn. Pvt. Ltd

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions: All the authors have contributed equally to the research work.

Ethical Approval: Approved

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How to cite this article: Deo V, Shrikhande B, Ganu G et.al. A randomized, placebo controlled clinical trial to evaluate the efficacy and safety of HFPM-01 in improving pain, stiffness, and inflammation in patients suffering from knee osteoarthritis. *International Journal of Research and Review. 2021; 8(4): 1-11. DOI: https://doi.org/10.52403/ijrr.20210401*

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