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A Randomized Placebo-Controlled Double-Blinded Study to Assess the Efficacy of Turmeric-Boswellia formulation PFK300 (Rhuleave-K) in Adult Subjects with Acute Musculoskeletal Pain

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Abstract
Background*: Musculoskeletal pain is very common around the world. The study was done to determine the efficacy of the formulation made of turmeric and Boswellia extract (PFK300, Rhuleave-K®) for acute musculoskeletal pain.*
Materials and Methods*: In this prospective randomized double-blind study, 40 subjects were randomized in an allocation concealed 1:1 ratio to receive a single dose of 500 mg of PFK300 (Rhuleave-K®) or placebo. The primary outcome was the sum of pain intensity difference at 6 hours (SPID6) evaluated by the Numerical Rating Scale (NRS) and total pain relief (TOTPAR6) evaluated by categorical pain relief scale (PRS) every 30 minutes up to 6 hours. The secondary outcomes were perceptible and meaningful pain relief (PPR and MPR) and sensory and affective pain using McGill Pain Questionnaire-Short Form (MPQ-SF).*
Results*: There was a significant difference in the pain intensity in PFK300 (test) group compared to the placebo from 270 minutes onwards. The sum of pain intensity difference (SPID6) and the area under the pain intensity effect curve (AUE6) was highly significant in the test group at the end of 6 hours of study when compared to placebo (p<0.0001). In the cumulative responder analysis, 62% improvement was observed in the test group and 2.7 % improvement in the placebo group. There was a statistically significant difference in the total pain relief (TOTPAR6) between the groups (p<0.001). The perceived pain relief (RMST) experienced in the test group (268.75 min) was significantly better (p=0.003) than in the placebo group (312 min). In the test group, the quality of pain relief was significant in the sensory (p=0.001) and affective (p=0.01) domains, and the total score of the McGill Pain Questionnaire (p=0.001) whereas the placebo group had no significant change. The Visual Analogue Scale (VAS) and Present Pain Index also showed a significant difference (p=0.001) in the test group whereas the placebo group had shown no significant change.*
Conclusion: *The study concluded that PFK300 (Rhuleave-K®) at the dose of 500 mg had significant pain relief properties with a cumulative pain relief response of 62%.*
Key Word*: Turmeric; Boswellia; Musculoskeletal pain; Pain measurement; Pain intensity; Pain relief.*

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I. Introduction

Acute musculoskeletal pain (MSP) is a sudden onset of pain affecting the muscles, joints, tendons, ligaments or nerves and differentiated from pain due to serious causes such as tumors, fractures, or infections, and systemic and neurological factors.[1] The types of pain are named according to the region of affection such as back pain, neck pain, shoulder pain, elbow pain, buttock pain, hip pain, knee pain, and ankle pain.[2] The prevalence of musculoskeletal conditions increases with age and low back pain was one of the main reasons for a premature exit from the workforce. Musculoskeletal conditions are also the biggest contributor to years lived with disability (YLDs) worldwide with approximately 149 million YLDS, accounting for 17% of all YLDs worldwide.[3]

Currently, the pharmacological approach to pain management is the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, and acetaminophen.[4] Natural therapies such as botanical polyphenolic constituents are effective inhibitors of pro-inflammatory enzymes, thus preventing formation of toxic cytokines generated through inflammatory reactions. Natural therapies are preferred by most due to their safe and effective support in inflammation and pain, besides having a track record of centuries of use in traditional medicine.[5]

Curcuma longa (*Curcuma longa* L., Zingiberaceae) or turmeric is a rhizomatous herbaceous perennial plant. Turmeric powder is approximately 60–70% carbohydrates, 6–13% water, 6–8% protein, 5–10% fat, 3–7% dietary minerals, 3–7% essential oils, 2–7% dietary fiber, and 1–6% curcuminoids. Phytochemical components of turmeric include diarylheptanoids, which occur from numerous curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin.[6] The curcuminoids (curcumin, de-methoxy curcumin, and bis-demethoxy curcumin) and volatile oil present in the turmeric (*Curcuma longa*) rhizomes are responsible for a wide range of biological activities.[6,7] The principal active component of turmeric is curcumin. Curcumin can modulate several different transcription factors, cytokines, growth factors, kinases, and other enzymes.[8]

Boswellia is a genus of trees in the order Sapindales, known for their fragrant resin which has many pharmacological uses. The distributions of the species are primarily associated with the tropics. *Boswellia serrata* is a medium to large-sized branching tree and is native to tropical regions of Africa and Asia. *Boswellia serrata* has been used for a variety of therapeutic purposes such as cancer, inflammation, arthritis, asthma, psoriasis, colitis, and hyperlipidemia.[9] *Boswellia serrata* has been used in ancient traditional medicines against arthritic pain and other inflammatory and chronic degenerative diseases.[10] Boswellic acids are the biologically active constituent derived from its gum resin. Various clinical trials in India and abroad have proved that Boswellic acids are excellent anti-inflammatory agents which can work against osteoarthritis, rheumatoid arthritis, and low back pain.

The research question of the present study was whether a single capsule of 500 mg of the pain formulation PFK300 *(Rhuleave-K®)* which is a combination of turmeric, boswellia, and sesame oil is effective in acute musculoskeletal pain management.

II. Material And Methods

Study Design

This single-center study with a randomized placebo-controlled design enrolled 40 healthy subjects with acute MSP. The study used a balanced randomization with 1:1 allocation. The study protocol was approved by the Institutional Ethics Committee of Pushpanjali Hospital and Research Centre, Agra, and no amendments to the accepted protocol were done after starting the study. The study was conducted from February 2020 to January 2021 in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization – Good Clinical Practice guidelines and was registered in the Clinical trial registry of India (CTRI/2020/02/023335).

Subjects Inclusion criteria/Exclusion criteria

The study included healthy male and female subjects aged 18-65 years with acute musculoskeletal pain following physical excercise with a resting Numerical rating scale (NRS) of 5 or above on a 0-10 scale, which occurred within 24 hours before presenting at the site. All subjects provided voluntary written informed consent before initiating the study procedures. Informed consent and eligibility assessments were taken by the principal investigator.

Those subjects with acute muscle spasms requiring parenteral therapy or surgery, or hospital admission for management of painful acute soft tissue injury of the upper or lower extremity, including acute injuries of ligaments, tendons, or muscles, or Grade 2 and 3 sprain or strain; or with history of osteoarthritis or rheumatoid arthritis, gastro-intestinal hemorrhage or perforation, or other critical conditions like cardiovascular, renal, pulmonary, endocrine, or neurological disorders, or consuming any Ayurvedic, Siddha, Unani or other products for pain and inflammation in the week prior to the study were excluded.

Intervention and Dosing

The subjects who met all the inclusion and exclusion criteria were randomized to receive either PFK300 (Rhuleave®-K) 500 mg softgel capsule (Batch No. MSP-XY02/20-21) or a matching placebo 500 mg (MSP-XX02/19-20) manufactured by Arjuna Natural Pvt. Ltd, Kerala, India. Rhuleave®-K (PFK300) contains Turmeric (*Curcuma longa* L.) extract, *Boswellia serrata* extract, and black sesame (*Sesamum indicum*) seed oil. Turmeric rhizomes and *Boswellia serrata* gum resin were extracted using ethyl acetate and their actives - curcuminoids and boswellic acids were uniformly solubilized in the sesame seed oil using a proprietary technology. PFK300 was standardized to contain 26.6% curcuminoids and 1% acetyl keto-boswellic acids and was encapsulated in size '0' vegetarian reddish-brown colored soft gel capsules.

Randomization, blinding, and unblinding

The randomization sequence was generated by an independent statistician using the WinPepi version 11.65 (2016) software. The master randomization list with PFK300 and placebo in a 1:1 ratio was allocation concealed using alphanumeric codes. The identities of the investigational products were blinded by the usage of similar size, colour, packaging, and labeling. The investigational products were enclosed in similar opaque

bottles and identified only by the alphanumeric codes. The alphanumeric code list was given to the pharmacist for serial dispensation. No other study staff was involved in the dispensing process. The investigators and the subjects were blinded to the identity of the investigational products.

Outcome Assessments

The primary outcome was total pain relief at the end of 6 h (TOTPAR6) using the pain relief scale (PRS) and a change in the sum of pain intensity difference at the end of 6 h (SPID6). The secondary efficacy outcomes were onset of analgesia measured using the double stopwatch method and quality of pain relief by a short form of McGill questionnaire.

Numerical pain rating scale (NRS)

The NRS is an 11-point scale in which 0 represents 'no pain' and 10 represents the worst pain possible. A rating score of 1-4 is considered mild, 5-6 is moderate and 7-10 is severe pain. NRS was taken at 30 min intervals up to for calculating SPID6.

Pain relief scale (PRS)

The pain relief scale is a categorical scale having a positive progression from 'No relief', 'A little relief', 'Some relief', 'A lot of relief' to 'Complete relief' (coded 0 to 4). TOTPAR is the area under the time-analgesic effect curve for a given time. PRS was taken at 30 min intervals up to 6 h for calculating TOTPAR6.

Onset to analgesia

The onset to analgesia was taken using the "double stopwatch" method. After dosing, two stopwatches were started simultaneously. The first stopwatch was stopped when the subject reported the first perception of pain relief (PPR). The second stopwatch was stopped when the subject felt complete pain relief called meaningful pain relief (MPR). The time to PPR and MPR was recorded in hours and minutes and when PPR / MPR was not reached within 6 h, it was censored at that time point.

Short form of McGill pain questionnaire (SF-MPQ)

The McGill Pain Questionnaire (MPQ) allows the subject to describe the quality and intensity of pain. The subject uses words to describe intensity (Sensory Domain); distress, discomfort, and the feeling associated with continuous or intermittent suffering (affective domain). SF-MPQ consists of 15 descriptors (11 sensory; 4 affective) which were rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Subjects also rated their present pain intensity (PPI) on a 0–5 scale (0 = No pain,1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, 5 = excruciating). Pain intensity was assessed on a 0-100 mm horizontal VAS, anchored with no pain as (left) and worst possible pain as (right). VAS measures were scored by measuring the distance in millimeters from the left anchor to the mark the subject made on the line.

Statistical analysis

The pain intensity difference (PID change from baseline, $PI_{baseline} - PI_{time}$) derived from NRS scale were analyzed using the linear mixed models for repeated measures. The SPID and AUC were calculated and analyzed using Mann Whitney test. Treatment differences from control (Placebo) were estimated from the least-squares mean (LSM) with 95% confidence intervals and associated 2-sided p-values. SPID and AUC were calculated at 180 and 360 minutes.

The cumulative proportion of responder's analysis (CPRA) was done according to Farrar *et al*. The analysis used AUC bootstrapping with 5000 iterations and 95% confidence intervals (CI). The CPRA graphs present the cumulative proportion of subjects who achieved a specific response rate (or percentage) as an improvement from baseline, determined by levels of response from lowest to highest. The responders were defined as subjects with improvement from baseline greater or equal to zero. The non-responders were defined as subjects with a change from baseline less than 0. All calculations were performed using R 3.6.3.

For the onset of analgesia, PPR and MPR were analyzed by Kaplan Meier (KM) curve and compared using log rank test. The test statistic was compared with a χ^2 distribution with 1 degree of freedom. Median time to onset, Restricted Mean Survival Time (RMST) was calculated from the KM analysis. TOTPAR between the groups was analyzed using Mann-Whitney U test. Wilcoxon Signed-Rank Test and paired t-test was done in SF-MPQ, VAS, PPI for within group analysis.

III. Result

Forty subjects were screened and enrolled in the study. The study flow diagram is represented in Figure 1. The presenting conditions reported by subjects at the time of screening were low back pain (n=8), upper back pain (n=7), generalized body pain (n=6), shoulder pain (n=12), neck pain (n=5), thigh pain (n=6), joint pain (n=8) and arm pain (n=4). Most of the subjects have reported more than one condition. There was no significant difference between the baseline data of PFK300 and placebo groups (Table 1).

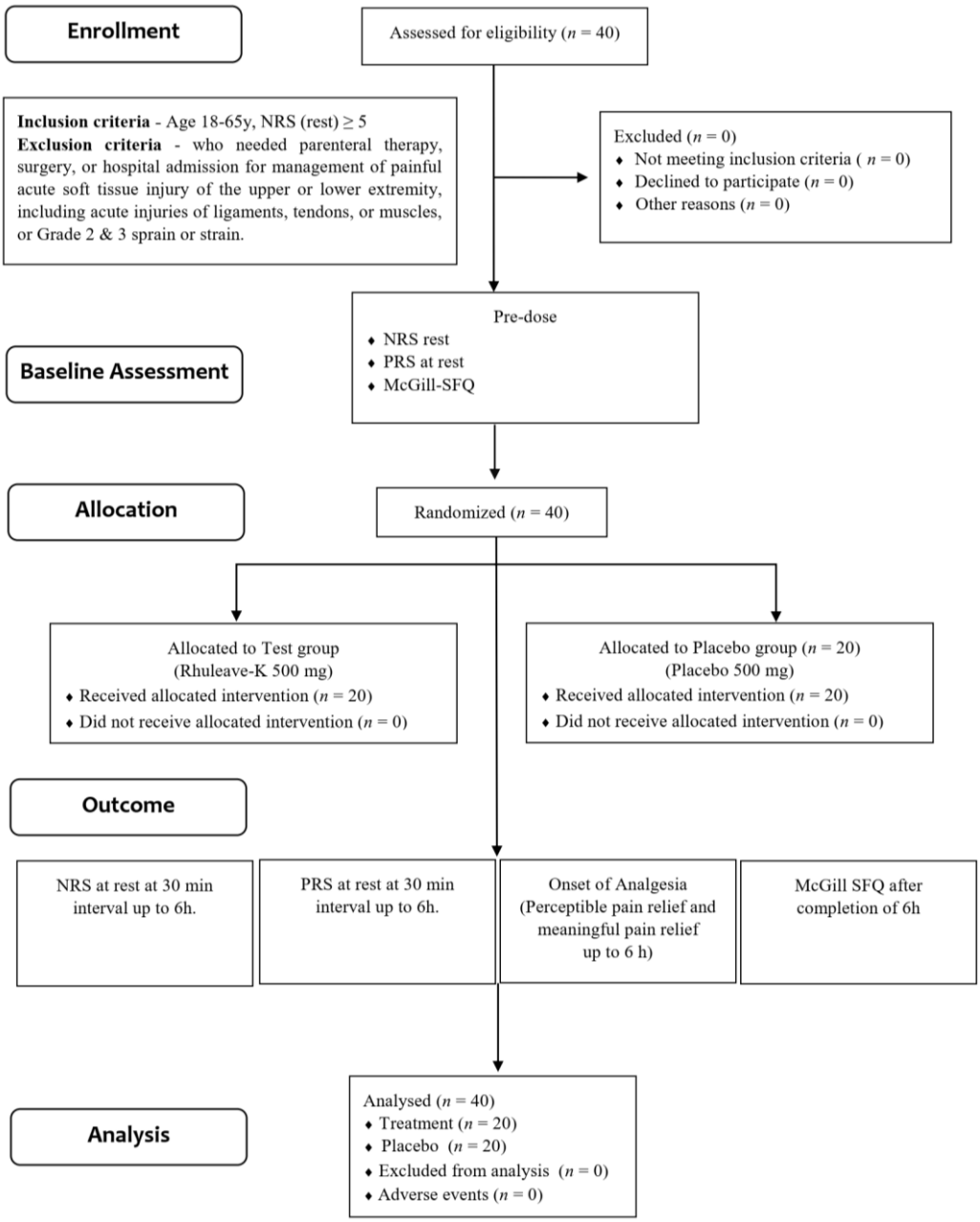

Figure 1. Study flow diagram

Table 1. Comparison of Baseline demographic variables of PFK300 and placebo groups

Variables	PFK300	Placebo	p value*
	Mean ± SD	Mean ± SD	
Age (years)	33.6 ± 9.10	33.4 ± 13.47	0.5548
Height (cms)	172.3 ± 9.07	171.4 ± 8.32	0.7262
Weight (kg)	71.8 ± 9.58	71.6 ± 12.53	0.9785
Systolic BP (mm Hg)	121.5 ± 8.13	116.5 ± 8.75	0.1004
Diastolic BP(mm Hg)	74.8 ± 5.00	73.5 ± 6.71	0.653
Oral Temperature (°F)	98.2 ± 0.25	98.1 ± 0.34	0.3305
Pulse Rate (beats/min)	86.7 ± 5.70	84 ± 4.63	0.109#
Respiratory Rate (beats/min)	21.1 ± 1.02	20.9 ± 1.02	0.5461
NRS	6.05 ± 0.945	6.3 ± 0.923	0.3587

*Wilcoxon rank test.
Welch-Satterthwaite t-test

Table 2. Numerical pain intensity using NRS over time of 6 h

Time (min)	PFK300	Placebo
	Mean ± SD	Mean ± SD
Pre Dose	6.05 ± 0.95	6.3 ± 0.92
30	6.05 ± 0.95	6.3 ± 0.92
60	6.05 ± 0.95	6.3 ± 0.92
90	6.05 ± 0.95	6.3 ± 0.92
120	6.05 ± 0.95	6.3 ± 0.92
150	6.05 ± 0.95	6.3 ± 0.92
180	5.95 ± 0.89	6.25 ± 0.97
210	5.85 ± 0.99	6.2 ± 1.06
240	5.65 ± 1.04	6.15 ± 1.14
270	5.55 ± 1.05	6.15 ± 1.14
300	4.75 ± 0.85	6.15 ± 1.14
330	3.6 ± 0.75	6.15 ± 1.14
360	2.3 ± 0.92	6.15 ± 1.14

Pain intensity assessed using the Numerical rating scale is represented in Table 2. Figure 2 shows that there is a considerable decrease in the pain intensity in PFK300 group compared to the placebo.

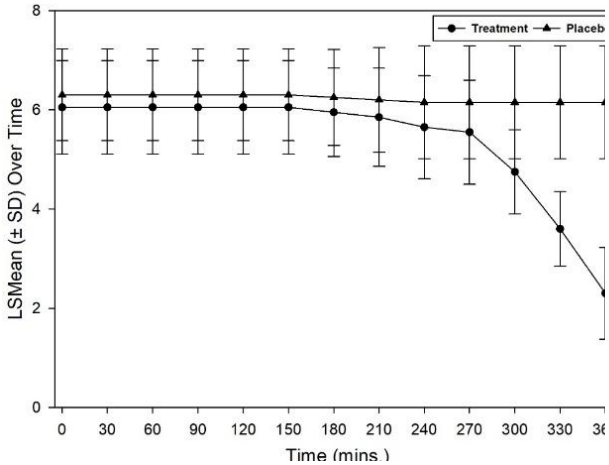

Figure 2. Comparison of mean pain intensity (NRS) over time for the two groups

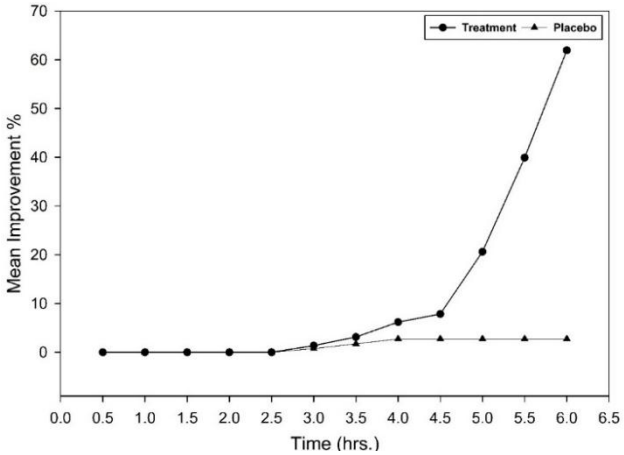

Figure 3. Cumulative responder analysis plot with a mean improvement in pain relief over time for Placebo and PFK300.

Sum of pain intensity difference (SPID6) and the area under pain intensity effect curve (AUE6) showed a significant difference at 360 min when compared to placebo ($p<0.0001$) (Table 3). In the cumulative responder analysis, 61.93% of improvement was observed in the PFK300 group while it was 2.7 % improvement in placebo (Table 4, Figure 3).

Table 3. Comparison of sum of pain intensity difference (SPID) at 180 min and 360 minutes for the two groups.

	SPID 180	SPID 360	AUE 180	AUE 360
PFK300 (Mean ± SD)	3 ± 9.23	261 ± 64.64	1.5 ± 4.62	204.75 ± 59.46
Placebo (Mean ± SD)	1.5 ± 6.71	27 ± 66.66	0.75 ± 3.35	24.75 ± 61.23
LSM Diff from Placebo	-1.5	-234	-0.75	-180
95% CI	(-21.23, 18.23)	(-253.73, -214.27)	(-18.56, 17.06)	(-197.81, -162.19)
p-value, 2-sided	0.881	<0.0001	0.9339	<0.0001

AUE = Area under effect curve

Table 4. Cumulative responder analysis with percentage improvement of pain relief for PFK300 and placebo groups.

Time (h)	AUC		% Improvement			95% CI of Diff	
	PFK300	Placebo	PFK300	Placebo	Difference	LCL	UCL
0.5	0.00	0.00	0.00	0.00	0.00	-	-
1	0.00	0.00	0.00	0.00	0.00	-	-
1.5	0.00	0.00	0.00	0.00	0.00	-	-
2	0.00	0.00	0.00	0.00	0.00	-	-
2.5	0.00	0.00	0.00	0.00	0.00	-	-
3	136.86	75.826	1.369	0.758	0.610	0.574	0.647
3.5	312.657	172.546	3.127	1.725	1.401	1.343	1.459
4	618.415	272.23	6.184	2.722	3.462	3.380	3.544
4.5	783.928	272.23	7.839	2.722	5.117	5.038	5.196
5	2061.87	272.23	20.619	2.722	17.896	17.829	17.964
5.5	3991.683	272.23	39.917	2.722	37.195	37.138	37.251
6	6193.353	272.23	61.934	2.722	59.211	59.135	59.287

The mean TOTPAR at 6 h was 198.0 for PFK300 and 31.5 for placebo. There was a statistically significant difference in the pain relief between PFK300 and placebo ($p<0.0001$) at 360 minutes (Table 5). The median survival time (perceptible pain relief) was 290 min for PFK300. The median for placebo was not estimatable due to too many non-responders. The RMST of PFK300 was 268.75 minutes compared to 312 minutes in placebo and pain relief was significantly better ($p=0.003$) than placebo (Table 6). The log-rank test shows that the difference between the PFK300 group and placebo group is highly statistically significant ($p<0.0001$).

Table 5. Total pain relief (TOTPAR) of PFK300 and placebo at the end of 6h.

Time (min)	PFK300	Placebo	
	Mean TOTPAR ± SD	Mean TOTPAR ± SD	p value
180	3.0 ± 9.23	6.0 ± 20.88	0.9794
360	198.0 ± 67.01	31.5 ± 79.36	<0.0001

Table 6. Onset of Analgesia - Perceptible Pain Relief (PPR)

	PFK300	Placebo
Symptom resolved (n = 40)	20	3
Median PPR (minutes)	290	NE
Restricted Mean Survival Time (RMST ± SE) (minutes)	268.75 ± 10.45	312.0 ± 9.81
RMST (between groups analysis)	p = 0.003	

The quality of pain assessed by McGill questionnaire was analyzed using the Wilcoxon and paired t test (Table 7). There was a significant difference in the sensory and affective domain as well total score of MPQ in PFK300

group whereas the placebo group had no significant change. In the VAS and PPI also the PFK300 has significant difference whereas the placebo was without significant change.

Table 7. McGill Quality of Pain Relief Pre-Post analysis between PFK300 and placebo

		Mean	Mean Difference ± SE	t value	p-Value
Sensory- PFK300	Predose	9.55	4.1 ± 0.49	8.38	0.001
	Postdose	5.45			
Sensory- Placebo	Predose	9.3	-0.25 ± 0.49	-0.51	0.62
	Postdose	9.55			
Affective- PFK300	Predose	1.85	0.85 ± 0.31	2.7	0.01
	Postdose	1			
Affective- Placebo	Predose	2.3	-0.05 ± 0.31	-0.16	0.88
	Postdose	2.35			
Total score MPQ Response-PFK300	Predose	11.4	4.95 ± 0.45	11.1	0.001
	Postdose	6.45			
Total score MPQ Response-Placebo	Predose	11.6	-0.3 ± 0.45	-0.67	0.51
	Postdose	11.9			
VAS (mm)- PFK300	Predose	64	20.5 ± 2.83	7.25	0.001
	Postdose	43.5			
VAS (mm)-Placebo	Predose	67.85	-2.35 ± 2.83	-0.83	0.41
	Postdose	70.2			
PPI - PFK300	Predose	2.45	1.05 ± 0.19	5.54	0.001
	Postdose	1.4			
PPI - Placebo	Predose	2.7	-0.05 ± 0.19	-0.26	0.79
	Postdose	2.75			

IV. Discussion

The primary objective of conducting the present study was to substantiate the observation that PFK300 *(Rhuleave-K®)* a novel combination of *Boswellia* extract, turmeric extract and sesame seed oil reduces pain intensity in participants with musculoskeletal pain following exercise. Earlier studies indicate that 3-O-Acetyl-11-keto-beta-boswellic acid (AKBA) is the most active principle present in the Boswellia extracts, which mainly contributes the anti-inflammatory activities of this herbal extract by inhibiting 5-lipoxygenase activity.[11,12] To date, the anti-inflammatory and anti-arthritic efficacy of different forms of Boswellia extracts have been established in various models either *in vitro* or *in vivo* or in clinical studies.[13–17] However, studies indicate that upon oral administration, Boswellia extracts exhibit poor intestinal absorption of AKBA and poor bioavailability which limits its anti-inflammatory efficacy.[18,19] A combination of turmeric and boswellia extracts unlike the commonly used NSAIDs and COX2 inhibitors, by virtue of the natural property of ingredients like curcuminoids and boswellic acids, inhibit the biosynthesis of both prostaglandin (PGE2) and leukotrienes (LTB4, LTC4, LTD4, LTE4)[20] and sesamin could inhibit cyclooxygenases which is responsible for the production of prostanoids.[21] The inhibition of both cyclo-oxygenase and lipo-oxygenase pathway is a unique property exhibited by this synergistic combination. NSAID's inhibit whole of prostaglandins including PGE1, which play a key role in preventing vascular thrombosis.[22] This combination contrary to this enhance the production of cell wall prostacycline by 37%. NSAID's inhibit PG synthesis through cyclo-oxygenase pathway which leaves the excess of arachidonic acid for lipo-oxygenase to convert into leukotrienes. The current combination with its dual mechanism of action inhibits both cyclo-oxygenase and lipo-oxygenase pathways to inhibit both prostaglandins and leukotrienes. Unlike some conventional drugs, the combination does not cause gastric irritation, bronchospasm, hepatic or renal toxicity. The encouraging anti-inflammatory and analgesic property and other benefits of all natural agents being hepato/reno protective apart from being an anti-oxidant reemphasize the fact that the combination of turmeric, boswellia extract, and sesamin is a promising analgesic and anti-inflammatory agent. The outcome measures of pain intensity (NRS, SPID6), Pain relief (PRS,

TOTPAR6) and sensory and affective domain status (SF-MPQ, VAS and PPI) reveal that the study medication PFK300 alleviates pain and improves the psychological wellbeing of the participant.

Previous studies on the formulation of turmeric and Boswellia serrata extract in sesame oil yielded encouraging results. An open label study on 88 subjects with musculoskeletal pain in comparison to acetaminophen concluded that the formulation was not inferior to acetaminophen.[23] A randomized, double-blinded study on 232 subjects with exercise induced musculoskeletal pain against placebo found that the formulation with a dosage of 1000 mg had significant pain relief properties.[24] In comparison with the placebo, at the end of the study, the PFK300 supplemented group showed statistically significant improvements in all pain scores including VAS, PPI, PRS (TOTPAR6) and NRS (SPID6).

V. Conclusion

In conclusion, the present study validates the potential analgesic efficacy of PFK300 and establishes the fast onset of pain relief action of PFK300 in participants with acute musculoskeletal pain. PFK300 at the dosage of 500 mg significantly improved pain intensity and perceptible pain relief was achieved as early as four hours of treatment. This study bears potential promise in favor of PFK300 as useful alternative management of acute musculoskeletal pain in humans.

Declarations

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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