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ORIGINAL RESEARCH

A Randomized Placebo-Controlled Dose-Response Trial of Muvz™ for Knee and Low-Back Support in Physically Active Adults

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Purpose: The current study aimed to investigate the dose-response efficacy and safety of Muvz™ (E-PR-01, a blend of *V. negundo* and *Z. officinale*) in 400 mg (High-dose [HD]) and 200 mg (Low-dose [LD]) of daily dose in physically active adults in 90 days.

Patients and Methods: The study included 157 adults aged 40–60 having knee/low back joint discomfort. The primary outcome was an enhancement in the overall musculoskeletal health in 90 days. Secondary outcomes included assessing the joint discomfort following physical activity, range of motion, quality of life, and the consumption of rescue medication.

Results: E-PR-01 notably enhanced musculoskeletal health in a dose-dependent manner compared to placebo within 30 days ($p<0.0001$), with effects persisting through day 90 and demonstrated clinically significant difference by 13 and 10 units in the HD and LD groups, respectively. Joint discomfort reduced significantly in both the E-PR-01 groups by day 90 ($p<0.0001$). Furthermore, both doses of E-PR-01 improved the range of motion of the assessed joint ($p<0.05$) and enriched participants' overall quality of life ($p<0.05$) at the end of the study.

Conclusion: The study finds E-PR-01 effective for improving overall joint health, with the higher dose showing greater efficacy. These findings align with the earlier studies of E-PR-01 for knee and low back discomfort.

Keywords: low back pain, knee joint, *Zingiber officinale*, range of motion, placebo-controlled, Vedic Lifesciences, dietary supplement

Introduction

The musculoskeletal system is a dynamic and complex matrix consisting of a variety of tissue types of several cellular components. Adequate functioning of this system as a whole requires interactions between different tissue types. With increasing age and repeated movements, people face new challenges in maintaining musculoskeletal health. This is due to the complications in the interactions between different components of the musculoskeletal system by the aging process and changing health status.[1–3] Degenerative changes of articular cartilage, and intervertebral discs are the salient features of an aging skeleton and lead to joint discomfort leading to arthralgia and eventually restricted mobility. Aging of skeletal muscle is marked by various structural and functional changes, which contribute to greater physical limitations and an increased risk of musculoskeletal conditions.[4] A recent analysis of Global Burden of Disease (GBD) 2019 data showed that approximately 1.71 billion people worldwide are affected by conditions like osteoarthritis, neck pain, low back pain and injuries.[5] Amongst these, low back pain is known to be the primary contributor to the overall musculoskeletal global burden.

There are several risk factors for developing non-specific low back discomfort including low physical activity levels, sedentary lifestyle, smoking, obesity and high physical stress at work. The incidence of these risk factors is rising, thereby leading to an increased prevalence of low back discomfort. An imbalance in the catabolic and anabolic pathways

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also leads to disruption in the cartilage tissue integrity and degeneration.[6] According to a notification from the World Health Organization (WHO), in 2020, roughly 1 in 13 individuals (estimated 619 million individuals), experienced low back discomfort. This marked a 60% rise from 1990, with projections suggesting an additional increase to approximately 843 million by 2050. Occasional and chronic low back pain impacts the capacity of individuals to engage in social, family and work-related activities leading to negative consequences on their mental well-being and thus may impose significant physical, emotional or economic burdens on families, communities, and healthcare systems.[7] Low back discomfort also serves as the primary cause for premature departure from the workforce. Thus, the societal ramifications of early retirement, including direct healthcare expenses and indirect costs such as absenteeism or reduced productivity are significant.[8] The currently recommended interventions (pharmacotherapies, dietary supplementation, physical therapy or other) primarily focusing on symptomatic relief, do not target the basic pathology with inadequate polymorphism.[9] Therefore, product development is continual to seek safer means of maintaining healthy joint function and musculoskeletal health. Dietary ingredients and supplements from a variety of natural origins have shown promising effects in previous clinical studies.[10–12]

Vitex negundo (*V. negundo*) has been recognized in Ayurveda as a potent botanical with strong anti-inflammatory and analgesic properties.[13] Its pain-suppressing activity is mediated via Prostaglandin (PG) synthesis inhibition, antihistamine, membrane-stabilizing and antioxidant activities.[14,15] *Zingiber officinale* (Ginger) rhizome is a widely recognized Asian spice renowned for its historical use as an anti-nausea, anti-inflammatory and analgesic agent.[16] Ginger has been granted "generally regarded as safe (GRAS)" status by the US Food and Drug Administration. It has been recognized in the scientific literature as a potential therapeutic agent owing to various metabolic pathways impact including but not limited to inhibition of COX (cyclooxygenase), LOX (lipoxygenases) and PG syntheses, antioxidant activity, inhibition of several cytokines and vanilloid nociceptor competitive agonism.[17–21] A recent review of clinical trials of ginger concluded that the use of ginger for its pain-lowering effect is safe and may have efficacy.[18] Moreover, both *V. negundo* and *Z. officinale* have a long history of safe consumption in traditional phytomedicine.

Muvz™ (E-PR-01) is a proprietary blend of *V. negundo* and *Z. officinale*. This product has been previously tested in multiple clinical studies[22–24] targeting different domains of musculoskeletal health. In the pilot study, the E-PR-01 product at a dose of 200 mg/day, demonstrated a clinically meaningful reduction in activity-induced knee joint discomfort.[22] The confirmatory study validated this outcome finding, while also noting a high responder rate to the product.[23] Further, the E-PR-01 product administered at a dose of 400 mg/day, has shown a statistically significant decrease in low back discomfort and related disability within seven days of initiation and was further potentiated at day 30.[24] No safety concerns were observed during these studies and E-PR-01 improved joint discomfort. The significant effect of the product on discomfort prompted the evaluation of a lower dose of the E-PR-01 product (200 mg once daily). A longer duration study was indicated to explore the safety as well as habituation effect. Therefore, based on the previous data, doses of 400 mg/day (High-dose [HD]), as well as a dose of 200 mg/day (Low-dose [LD]), were selected for the present 90-day study.

The current study primarily was conducted to evaluate the efficacy of E-PR-01 in improving the overall musculoskeletal health of individuals experiencing joint discomfort and subsequently decreased functional ability during physical activity. Additionally, the impact of the investigational product (IP) on the range of motion (ROM) and quality of life was also assessed. Also, the impact of the IP on the concurrent usage of analgesics was evaluated.

Materials and Methods

Study Design

This study was a randomized, placebo-controlled, parallel-group, double-blind, multicentre clinical study to evaluate the effects of 90 days' administration of E-PR-01 on musculoskeletal health. The study was conducted between April 2023 and January 2024 at six sites in the state of Maharashtra, India in the clinics of orthopedic doctors.

Ethical Considerations

This study was set up and conducted to comply with the Declaration of Helsinki, ICH-GCP, and Ethical Guidelines for Biomedical Research on Human Participants, 2017, issued by the Indian Council of Medical Research, India. The study protocol was approved by a central ethics committee, Harmony Ethical Research Committee, Maharashtra, India (Reg. No. ECR/1411/Inst/MH/2020) and Muktai Hospital Ethics Committee (Reg. No. ECR/251/Inst/MH/2013/RR-19). This study was registered on clinicaltrials.gov (NCT05825222) as well as Clinical Trials Registry India (CTRI/2023/03/051157). The investigators explained the objectives, procedures, risks, and benefits involved in the study to all the participants. Only participants willing to give voluntary written informed consent were recruited for the study. The study report conformed to the Consolidated Standard Reporting of Trials (CONSORT) guidelines.[25]

Participants

Inclusion Criteria

The study included adults aged 40–60 years having Body Mass Index (BMI) ≥24.9 and ≤29.9 kg/m^2, with a history of knee and/or low back discomfort aggravation on moderate physical activity (squatting, walking, running and cycling). The participants were included in the study if they met one of two criteria: either a low back pain score or knee joint pain score ≥60 on a 100-point Pain–Numeric Rating Scale (P-NRS)[26] after completion of 4 sets of five-repetition sit-to-stand tests. P-NRS is the pain rating that indicated the pain at the moment when the participant completed the protocol-specific physical activity. Participants rated inferior musculoskeletal health status due to knee or low back joint discomfort[27] as assessed using the Musculoskeletal Health Questionnaire (MSK-HQ)[28] developed by the Oxford University Innovation and with moderate physical activity level as per International Physical Activity Questionnaire (IPAQ-SF)[29] were included in the study.

Exclusion Criteria

Participants with debilitating pain at rest and those experiencing pain types other than joint pain, such as muscular, nervous, or acute injury-related pain were excluded from the study. For knee joint assessment, all screened participants with radiographical evidence of multiple moderate as well as large-sized osteophytes along with definite joint space narrowing, sclerosis, or bony deformity were excluded. If an X-ray report was not already conducted anytime within the last 7 days prior to screening, an X-ray was performed at screening for joint assessment.

Additional exclusion criteria included known cases of osteoporosis, neurological pain characteristics (shooting, burning, stabbing, or electric shock-like pain, tingling, numbness, or "pins and needles" sensation), insomnia, restless leg syndrome, uncontrolled hypertension, uncontrolled type II diabetes mellitus, and intake of any dietary supplement within 2 weeks of the screening visit. Furthermore, pregnant or lactating females and those on oral contraceptives were not included in the study.

Intervention

The investigational product E-PR-01, a patent-pending formulation of the *V. negundo* and *Z. officinale* extracts has been developed and manufactured by Enovate Biolife, Mumbai, Maharashtra, India. Each E-PR-01 capsule contained 200 mg of the proprietary blend. The placebo capsules consisted of 200 mg of microcrystalline cellulose (MCC) and were taken twice a day. The participants administered the assigned investigational products at a dose of either one capsule of E-PR-01 once a day (200 mg [LD]) or twice a day (400 mg [HD]) for 90 days. The blinding was maintained for the low dose by using a placebo capsule for the evening dose. The participants were randomized using the Interactive Web Response System (IWRS; Microsoft Azure) with a 1:1:1 allocation rate for E-PR-01 LD, E-PR-01 HD and placebo. The randomization chart was secured, saved, and maintained in the electronic trial master file with restricted access to only designated personnel. The participants, the research team, and the investigator were blinded to the sequence allocation. To preserve the blinding, the investigational products and the placebo capsules were matched for size, shape, color, and texture and packed in identical packaging.

The participants missing the intervention for only less than 10% of the prescribed regimen were considered IP compliant. The compliance was ascertained by maintaining a record of dispensed and returned products by counting the

number of capsules in the bottle. Acetaminophen (500 mg) was given as the rescue medication (RM) in case of intolerable pain, defined by a joint pain score ≥80 points on the P-NRS, due to physical activity. At each visit, the rescue medication consumed by each participant was also calculated. Any concomitant medication taken was recorded in the source document and Electronic-Case Record Form (e-CRF).

Study Outcomes

The primary outcome of the study was to assess the effect of two different doses of E-PR-01 on musculoskeletal health using the MSK-HQ. Oxford University Innovation developed the MSK-HQ questionnaire, comprising 14 items that allow reporting of musculoskeletal symptoms such as discomfort, pains and/or stiffness related to joint, back, neck, bone and muscle. The total MSK-HQ score is calculated as the sum of the scores of questions from 10 domains (pain, physical function, physical activity, pain interference with daily activities, independence, sleep and fatigue, emotional well-being, understanding of diagnosis and treatment, confidence to self-manage pain, overall impact of symptoms). The possible total score ranges from 0–56, with 56 being the best possible musculoskeletal health state and the recall period of the questionnaire is last two weeks.[28] Musculoskeletal health refers to the performance of the locomotor system, comprising intact muscles, bones, joints and adjacent connective tissues. In the current study, only participants with joint pain were included and hence the MSK-HQ score was relevant to joints. The minimal clinically important difference (MCID) for the change in MSK-HQ over 6 months is 5.5 units.[30] The secondary outcomes included assessing the effect on discomfort after physical activity by P-NRS. A clinically meaningful reduction of pain was analyzed at the end of the study and was defined as a 2-point decrease or a 30% reduction from baseline.[31] Furthermore, the range of motion (ROM) of the index joint was assessed by goniometry. Both the active (performed by the participant without any external force) and passive (performed by the participant with the application of an external force by the investigator) ROM of the index joint were measured. Additionally, the impact of the E-PR-01 was assessed on the quality of life of participants by the widely used EQ-5D-5L questionnaire. Also, the usage of the rescue medication was evaluated.

The safety of E-PR-01 was evaluated by the standard laboratory parameters [alkaline phosphatase (ALP), serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT)] at the randomization as well as the end of the study visit (day 90). Vitals (blood pressure and pulse rate) along with adverse events were monitored throughout the study.

Study Conduct

During the screening visit, the study procedures were thoroughly explained to the research participants in a language well understood by them, following which the study participant duly signed and dated informed consent. Participants self-administered a 100-point P-NRS to indicate the severity of pain they experienced at rest and after 4 sets of five-repetition sit-to-stand test. The joint with the highest score for P-NRS was considered as index joint and was assessed throughout the study. Participants were also instructed to self-administer IPAQ-SF to record their physical activity during the prior seven days. Subsequently, an X-ray of the index joint and a blood glucose test were performed. During the seven-day run-in phase, placebo capsules were administered and the participants reporting a decrease in pain severity after the above-mentioned exercises were considered placebo responders and were excluded from the study. Demographics and baseline characteristics, vitals (pulse rate and blood pressure), clinical examination, exercise, dietary, medical and medication history were recorded at the randomization visit. Participants' discomfort severity after the sit-to-stand test was reassessed at day 0 using the P-NRS scale and further at days 30, 60 and 90. Participants were also instructed to self-administer the IPAQ-SF, MSK-HQ, and EQ-5D-5L questionnaires at all visits. Additionally, the ROM of the index joint was measured using a goniometer at baseline and the end of the study.

Statistical Analysis

The sample size for the present study was calculated based on the previous study, assuming a difference of the mean of 3 for the MSK-HQ score between the E-PR-01 and placebo groups, with a standard deviation of 4 with alpha =0.05 and at 80% power.[24] Thus, the sample size of 48 per group having a degree of freedom=46 had been estimated. The null hypothesis was considered to be rejected in case E-PR-01 (LD and HD) was able to significantly improve

musculoskeletal health. The endpoint data were visually assessed for normality. All continuous variables have been summarized by presenting the number of participants, mean, standard deviation (SD), and 95% confidence interval (CI). Categorical variables have been presented as frequencies and percentages. For continuous data, paired t-tests or analysis of covariance (intervention as a factor and baseline as a covariate) were used where appropriate. Chi-square/Fisher's exact test was used for categorical variables to compare the data between groups. All statistical tests were performed with a significant level of 0.05 using the R/R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/version 4.0.5), and XLSTAT Statistical and Data Analysis Solution, New York, USA (https://www.xlstat.com./version 2021.3.1). The last observation carried forward (LOCF) was the primary method for missing data imputation and was performed only in those cases where at least one post-baseline assessment data was available. Utilizing an FDA-approved approach for statistical analysis of interventional studies, the safety and efficacy data were determined utilizing the Full Analysis Set (FAS) and Per Protocol (PP) data sets.[32]

Quality Assurance

The study was monitored and audited by the Contract Research Organization, Vedic Lifesciences (Mumbai, Maharashtra, India) to ensure compliance with the study protocol and with the ICH-GCP E6 (R2) guidelines.

Results

Out of 255 screened participants, 157 met the eligibility criteria and were randomized into the study. Of these, 152 participants had at least one observation completed after the administration of the study product and were considered as the Full Analysis Set. The detailed study participant disposition is presented in the CONSORT flowchart in Figure 1.

Demographics and Baseline Characteristics

The enrolled participants had a mean age of 48 years with an average BMI of 26.95 kg/m2. Also, there was no difference in the physical activity levels as assessed by the IPAQ – SF at baseline as well as at the end of the study ($p>0.05$) across the three groups. The demographics and baseline characteristics of the enrolled participants are summarized in Table 1.

Musculoskeletal Health

Participants with poor musculoskeletal health due to joint discomfort with MSK – HQ scores of ≤ 30 were enrolled in the study. At baseline, the mean scores of all three study groups were comparable with no statistically significant intergroup difference ($p=0.5348$). At days 30, 60 and 90, an improvement in musculoskeletal health as indicated by a significant increase in the mean scores of MSK – HQ was observed in the LD and HD of the E-PR-01, however, the dose-response with a greater increase of 13.73 (3.79) units was observed in the HD group as compared to the 10.36 (3.95) units in the LD group at day 90. This difference in the HD and LD groups was clinically significant as it achieved the known MCID of 5.5 units for MSK-HQ. At the same time, only a marginal increase of 1.98 (5.60) units was seen in the placebo group, and this difference of IP versus placebo was statistically significant in the HD and LD groups ($p<0.0001$) (Table 2 and Figure 2).

Additionally, in comparison to the placebo group, E-PR-01 in both doses exhibited significant improvements in various domains of the MSK – HQ which included pain during day and night ($p<0.0001$), physical function ($p<0.0001$), physical activity ($p<0.0001$), pain interference with daily activities ($p<0.0001$), independence to perform day to day activities ($p<0.0001$), sleep and fatigue ($p<0.0001$), emotional well-being (HD: $p<0.0001$; LD: $p=0.0001$), confidence in self-managing the pain (HD: $p=0.0042$; LD: $p=0.0060$) and overall impact of symptoms on quality of life ($p<0.0001$).

Furthermore, following a planned post-hoc analysis conducted separately for populations experiencing knee joint discomfort and low back discomfort, a notably significant enhancement ($p<0.0001$) in musculoskeletal health was observed by the conclusion of the study in both the high-dose and low-dose E-PR-01 groups compared to placebo within each cohort (Supplementary Tables S1 and S2). Thus, it can be inferred that the investigational product E-PR-01 exhibited equivalent effectiveness in both, the knee and low back joints. The applicability of the product E-PR-01 can thus be explored in different joints.

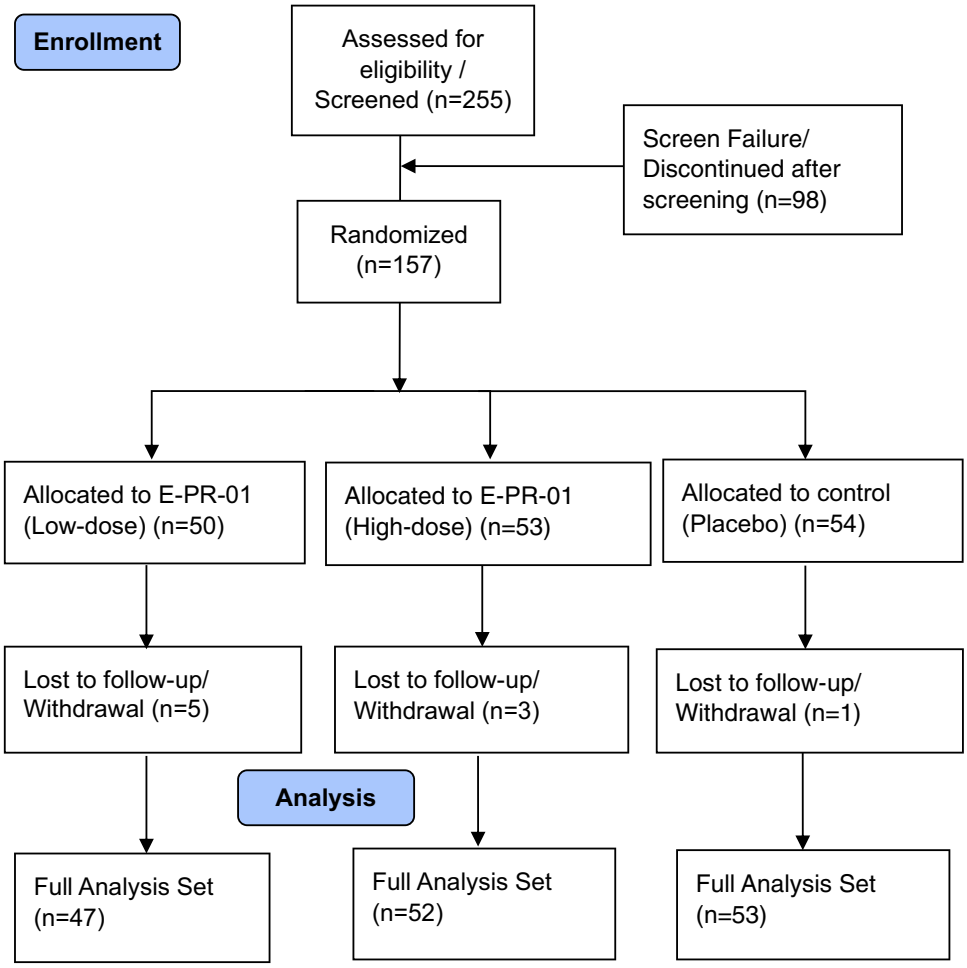

Figure 1 CONSORT flowchart. The CONSORT flowchart gives a detailed description of the participant disposition in the study.

Joint Discomfort

Joint discomfort was assessed using P-NRS and only participants with a score of ≥60 owing to physical activity were included in the study. At baseline, the mean scores of all three study groups were comparable with no statistically significant intergroup difference (p=0.4303). A reduction in pain indicated by the noteworthy decrease in P-NRS scores, was observed in both the LD and HD groups from as early as seven days. By the end of the study, there was a highly

Table 1 Demographic and Baseline Characteristics

Parameter	Statistics	E-PR-01 HD (N=53)	E-PR-01 LD (N=50)	Placebo (N=54)
Age (years)	Mean (SD)	48.58 (5.62)	48.26 (5.47)	49.74 (5.48)
	(Min, Max)	(40.00, 58.00)	(40.00, 60.00)	(40.00, 59.00)
Gender	Male	14 (26.42%)	11 (22.00%)	21 (38.89%)
	Female	39 (73.58%)	39 (78.00%)	33 (61.11%)
Height (metres)	Mean (SD)	1.57 (0.07)	1.57 (0.08)	1.58 (0.08)
	(Min, Max)	(1.47, 1.73)	(1.45, 1.76)	(1.37, 1.80)

(*Continued*)

Table 1 (Continued).

Parameter	Statistics	E-PR-01 HD (N=53)	E-PR-01 LD (N=50)	Placebo (N=54)
Weight (kg)	Mean (SD)	66.89 (6.76)	66.14 (6.34)	67.88 (7.57)
	(Min, Max)	(55.10, 82.85)	(58.00, 86.12)	(53.01, 89.30)
Body Mass Index (kg/m^2)	Mean (SD)	26.95 (1.15)	26.68 (1.23)	27.23 (1.13)
	(Min, Max)	(25.10, 28.78)	(25.02, 28.85)	(25.12, 29.16)
MSK-HQ total score	Mean (SD)	23.57 (3.24)	24.00 (3.50)	23.96 (3.10)
	(Min, Max)	(15.00, 30.00)	(17.00, 30.00)	(16.00, 30.00)
P-NRS score of index joint	Mean (SD)	76.23 (8.60)	78.20 (8.25)	77.41 (7.82)
	(Min, Max)	(60.00, 90.00)	(60.00, 90.00)	(60.00, 90.00)
Knee joint	N (%)	30 (56.60%)	27 (54%)	30 (55.56%)
Low back joint	N (%)	23 (43.40%)	23 (46%)	24 (44.44%)

Notes: For continuous variables, p-values were calculated using ANOVA. For categorical variables, the p-value was calculated using Chi-Square (C) test.
Abbreviations: MSK-HQ, Musculoskeletal Health Questionnaire; N, Number of participants; P-NRS, Pain-Numeric Rating Scale.

Table 2 Musculoskeletal Health

Parameters	Categories	E-PR-01 HD		E-PR-01 LD		Placebo		p-value
		Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	
MSK-HQ	**N**	52		47		53		
	Day 0	23.60 (3.27)	(22.69, 24.51)	24.32 (3.28)	(23.35, 25.28)	24.00 (3.11)	(23.14, 24.86)	[a]0.5348
	Day 30	28.92 (4.42)	(27.69, 30.15)	27.87 (4.42)	(26.57, 29.17)	25.43 (5.18)	(24.01, 26.86)	[a]0.0007
	Change from baseline at day 30	5.33 (4.07)	(4.19, 6.46)	3.55 (3.46)	(2.54, 4.57)	1.43 (3.82)	(0.38, 2.49)	[b]<0.0001
	[#]p value vs placebo	<0.0001		0.0098				
	Day 60	32.13 (6.19)	(30.41, 33.86)	29.49 (7.71)	(27.23, 31.75)	25.81 (7.09)	(23.86, 27.76)	[a]<0.0001
	Change from baseline at day 60	8.54 (5.98)	(6.87, 10.20)	5.17 (7.73)	(2.90, 7.44)	1.81 (6.08)	(0.13, 3.49)	[b]<0.0001
	[#]p value vs placebo	<0.0001 (T)		0.0193 (T)				
	Day 90	37.33 (3.76)	(36.28, 38.37)	34.68 (4.64)	(33.32, 36.04)	25.98 (7.06)	(24.04, 27.93)	[a]<0.0001 (A)
	Change from baseline at day 90	13.73 (3.79)	(12.67, 14.79)	10.36 (3.95)	(9.20, 11.52)	1.98 (5.60)	(0.44, 3.52)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				

Notes: [a]p-values were calculated using ANOVA Test (A). [b]p-values were calculated using Analysis of Covariance (ANCOVA) with treatment as factor and baseline as covariate. [#]p-values were calculated by comparing each treatment group to the placebo group using Dunnett's *T*-test with ANCOVA.
Abbreviations: CI, Confidence interval; MSK-HQ, Musculoskeletal Health Questionnaire; N, Number of participants; SD, Standard deviation.

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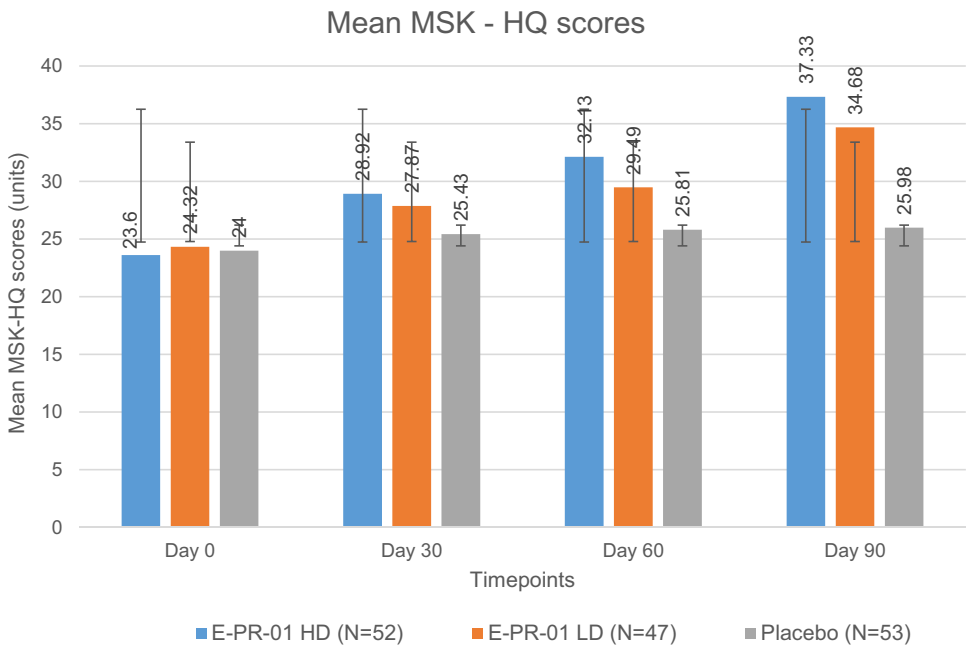

Figure 2 Mean MSK – HQ scores. The mean MSK-HQ scores in the three groups are indicated at all time points.
Abbreviation: MSK – HQ: Musculoskeletal Health Questionnaire.

significant reduction in the scores in both the E-PR-01 high dose [33.65 (14.95)] and low dose [26.38 (13.58)] as compared to the placebo group, which only experienced a minimal decrease [8.30 (17.84)]. This change in both E-PR-01 HD and LD groups was statistically significant compared to placebo ($p<0.0001$) by the end of the study (Table 3). Thus, 78% of participants in the HD group and 53% of participants in the LD group achieved the criterion of at least a 30% clinically meaningful reduction in pain scores from baseline (Figure 3).

Range of Motion

Flexion

As indicated in Supplementary Tables S3 and S4, all three study groups matched at baseline ($p>0.05$). At the end of the study, a significant mean increase of 4.84° (6.09) and 3.93° (4.28) was observed for the active flexion in the E-PR-01 HD and LD groups, respectively. In contrast, the placebo group showed a non-significant mean increase of 0.59 (4.94) degrees. Additionally, a statistically significant difference was observed when the E-PR-01 groups (HD and LD) were compared with the placebo group ($p<0.0001$ and $p=0.0037$, respectively) (Figure 4 and Supplementary Table S3).

In the case of passive flexion, at the end of the study, there was a statistically significant increase by 3.79 (6.30) and 2.71 (4.53) degrees in the E-PR-01 HD ($p<0.0001$) and LD ($p<0.0059$) groups, respectively, as compared to the placebo group which observed a decrease of 0.76 (5.78) degrees (Supplementary Table S4).

Extension

At baseline, the mean scores across all three study groups were comparable, with no statistically significant intergroup differences ($p>0.05$). At the end of the study, there was no significant change observed for the active or passive extension in either of the study groups.

Quality of Life

At the end of the 90 days, when compared to the placebo, the E-PR-01 groups (HD and LD), demonstrated a statistically significant improvement in all domains – mobility, self-care, usual activities, pain/discomfort and anxiety/depression of the EQ-5D-5L questionnaire as illustrated in Table 4 ($p<0.05$). Additionally, the EQ-Visual Analog Scale (VAS) also demonstrated a statistically significant improvement in the E-PR-01 groups when compared to placebo ($p<0.0001$).

Table 3 Pain Numeric Rating Scale Scores

Parameters	Categories	E-PR-01 HD		E-PR-01 LD		Placebo		p-value
		Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	
P-NRS scores	N	52		47		53		
	Day 0	76.15 (8.67)	(73.74, 78.57)	78.3 (8.16)	(75.90, 80.69)	77.17 (7.69)	(75.05, 79.29)	[a]0.4303
	Day 7	74.51 (9.23)	(71.91, 77.11)	74.68 (9.29)	(71.95, 77.41)	75.47 (7.48)	(73.41, 77.53)	[a]0.8342
	Change from baseline at day 7	−1.37 (6.01)	(−3.06, 0.32)	−3.62 (6.73)	(−5.59, −1.64)	−1.70 (5.09)	(−3.10, −0.30)	[b]0.2368
	[#]p value vs placebo	0.9971		0.2478				
	Day 30	65.58 (11.78)	(62.30, 68.86)	68.09 (12.27)	(64.48, 71.69)	72.45 (9.18)	(69.92, 74.98)	[a]0.0069
	Change from baseline at day 30	−10.58 (9.78)	(−13.30, −7.85)	−10.21 (8.21)	(−12.62, −7.80)	−4.72 (8.68)	(−7.11, −2.32)	[b]0.001
	[#]p value vs placebo	0.0013		0.0065				
	Day 90	42.5 (13.41)	(38.77, 46.23)	51.91 (13.45)	(47.96, 55.87)	68.87 (15.89)	(64.49, 73.25)	[a]<0.0001
	Change from baseline at day 90	−33.65 (14.95)	(−37.82, −29.49)	−26.38 (13.58)	(−30.37, −22.40)	−8.30 (17.84)	(−13.22, −3.38)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				

Notes: [a]p-values were calculated using ANOVA Test (A). [b]p-values were calculated using Analysis of Covariance (ANCOVA) with treatment as factor and baseline as covariate. [#]p-values were calculated by comparing each treatment group to the placebo group using Dunnett's *T*-test with ANCOVA.
Abbreviations: CI, Confidence interval; P-NRS, Pain Numeric Rating Scale; N, Number of participants; SD, Standard deviation.

Rescue Medication Consumption

As evident in Supplementary Table S5, the number of participants refraining from consuming the rescue medication was only 13% in the placebo group. In contrast, this abstinence was nearly threefold (36%) and twofold (29%) in the high-dose and low-dose groups, respectively, compared to the placebo at the end of the study. Importantly, a statistically significant difference was observed across all three groups (p=0.0138).

Safety Outcomes

No significant change was observed in the vitals and safety laboratory parameters of the enrolled participants, except for creatinine, in all study groups during the 90-day study period (Supplementary Table S6). The changes observed in creatinine can be attributed to the inter-individual variability and are, however, within the normal limits.

A total of thirty-seven adverse events were reported across all study groups. Among these, fifteen occurred in the E-PR-01 HD group, nine in the E-PR-01 LD group, and thirteen in the placebo group. All the adverse events were opined by the investigators as unrelated to the study product and they were resolved without any consequences (Supplementary Table S7).

Discussion

Musculoskeletal conditions commonly affect people even after living a physically active lifestyle and often lead to discomfort and pain in the back, neck, shoulders and knees. These problems impact the quality of life and have consistently been ranked for many years as the leading contributor to years lived with disability.[33] The current study evaluated the efficacy of E-PR-01 on musculoskeletal health using the Musculoskeletal Health Questionnaire over

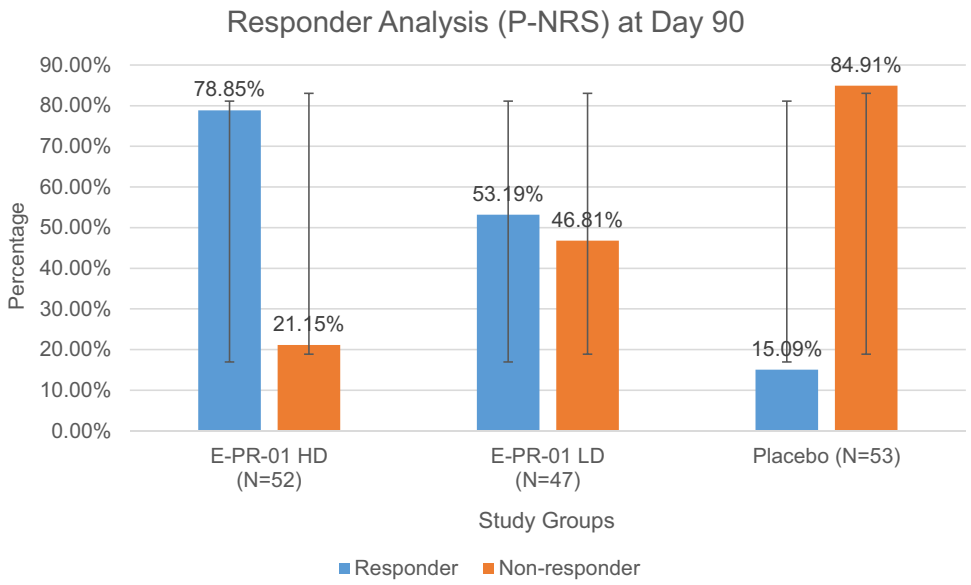

Figure 3 Responder Analysis (P-NRS) at Day 90. Responders were defined as participants achieving at least a 30% pain reduction as per P-NRS scores.
Abbreviation: P-NRS: Pain-Numeric Rating Scale.

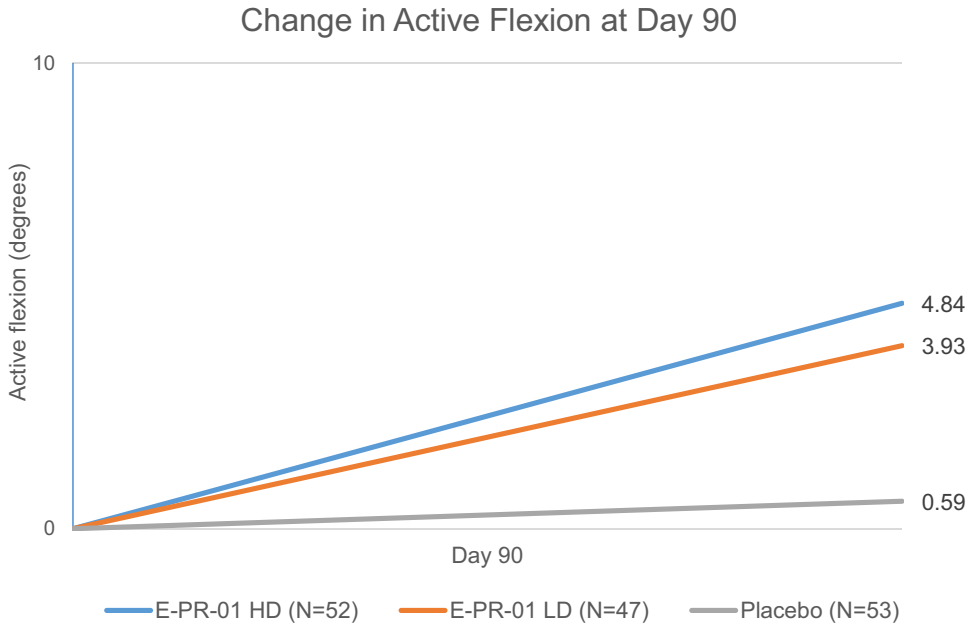

Figure 4 Change in Active Flexion at Day 90. The change in the degree of active flexion by goniometry at the end of the study in the three groups is indicated.

90 days (ie 3 months). In a study on United Kingdom primary care individuals with musculoskeletal pain, the MSK-HQ was utilized for its responsiveness and validity and the score showed strong discriminatory ability in identifying participants with improved MSK conditions.[28] In the current study, the improvement in musculoskeletal health was observed from day 30 itself and persisted consistently until the end of the study (90 days) in the E-PR-01 HD and LD groups. At the end of the study, an increase by 13.73 and 10.36 units was observed in the HD and LD groups, respectively. Thus, this change of MSK-HQ total score in both the E-PR-01 HD and LD groups was found to be not only statistically significant ($p<0.0001$) but also clinically relevant with the established minimal clinically important difference (MCID) of at least 5.5. A study conducted by Srivastava S et al reported that the intake of E-PR-01

Table 4 EQ-5D-5L Scores

Parameters	Categories	E-PR-01 HD		E-PR-01 LD		Placebo		p-value
		Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	
Mobility	**N**	52		47		53		
	Day 0	2.96 (0.56)	(2.81, 3.12)	2.83 (0.64)	(2.64, 3.02)	3.06 (0.57)	(2.90, 3.21)	[a]0.1586
	Day 30	2.46 (0.58)	(2.30, 2.62)	2.53 (0.5)	(2.38, 2.68)	2.89 (0.58)	(2.73, 3.05)	[a]0.0002
	Change from baseline at day 30	−0.50 (0.61)	(−0.67, −0.33)	−0.30 (0.59)	(−0.47, −0.13)	−0.17 (0.58)	(−0.33, −0.01)	[b]0.0004
	[#]p value vs placebo	0.0002		0.0223				
	Day 90	1.65 (0.59)	(1.49, 1.82)	1.94 (0.76)	(1.71, 2.16)	2.92 (0.76)	(2.72, 3.13)	[a]<0.0001
	Change from baseline at day 90	−1.31 (0.67)	(−1.49, −1.12)	−0.89 (0.7)	(−1.10, −0.69)	−0.13 (0.76)	(−0.34, 0.08)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				
Self-care	**Day 0**	2.63 (0.63)	(2.46, 2.81)	2.7 (0.55)	(2.54, 2.86)	2.68 (0.58)	(2.52, 2.84)	[a]0.8431
	Day 30	2.42 (0.57)	(2.26, 2.58)	2.45 (0.62)	(2.27, 2.63)	2.79 (0.72)	(2.59, 2.99)	[a]0.0053
	Change from baseline at day 30	−0.21 (0.78)	(−0.43, 0.00)	−0.26 (0.61)	(−0.43, −0.08)	0.11 (0.67)	(−0.07, 0.30)	[b]0.0030
	[#]p value vs placebo	0.0058		0.0067				
	Day 90	1.6 (0.69)	(1.40, 1.79)	1.77 (0.73)	(1.55, 1.98)	2.6 (0.79)	(2.39, 2.82)	[a]<0.0001
	Change from baseline at day 90	−1.04 (0.84)	(−1.27, −0.80)	−0.94 (0.79)	(−1.17, −0.70)	−0.08 (0.83)	(−0.30, 0.15)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				
Usual activities	**Day 0**	2.96 (0.63)	(2.79, 3.14)	2.85 (0.59)	(2.68, 3.02)	2.96 (0.71)	(2.77, 3.16)	[a]0.6192
	Day 30	2.56 (0.67)	(2.37, 2.74)	2.66 (0.52)	(2.51, 2.81)	3.02 (0.57)	(2.86, 3.18)	[a]0.0003
	Change from baseline at day 30	−0.40 (0.85)	(−0.64, −0.17)	−0.19 (0.74)	(−0.41, 0.03)	0.06 (0.66)	(−0.13, 0.24)	[b]0.0002
	[#]p value vs placebo	0.0001		0.0087				
	Day 90	1.79 (0.64)	(1.61, 1.97)	2.04 (0.62)	(1.86, 2.23)	2.92 (0.76)	(2.72, 3.13)	[a]<0.0001
	Change from baseline at day 90	−1.17 (0.83)	(−1.41, −0.94)	−0.81 (0.68)	(−1.01, −0.61)	−0.04 (0.65)	(−0.22, 0.14)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				

(*Continued*)

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Table 4 (Continued).

Parameters	Categories	E-PR-01 HD		E-PR-01 LD		Placebo		p-value
		Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	
Pain discomfort	**Day 0**	2.98 (0.75)	(2.77, 3.19)	3.19 (0.74)	(2.97, 3.41)	3.09 (0.60)	(2.93, 3.26)	[a]0.3263
	Day 30	2.58 (0.57)	(2.42, 2.74)	2.57 (0.54)	(2.42, 2.73)	2.98 (0.69)	(2.79, 3.17)	[a]0.0007
	Change from baseline at day 30	−0.40 (0.77)	(−0.62, −0.19)	−0.62 (0.80)	(−0.85, −0.38)	−0.11 (0.61)	(−0.28, 0.05)	b0.0002
	[#]p value vs placebo	0.0022		0.0003				
	Day 90	1.79 (0.61)	(1.62, 1.96)	2.04 (0.66)	(1.85, 2.24)	2.92 (0.73)	(2.72, 3.13)	[a]<0.0001
	Change from baseline at day 90	−1.19 (0.77)	(−1.41, −0.98)	−1.15 (0.66)	(−1.34, −0.96)	−0.17 (0.75)	(−0.38, 0.04)	[b]<0.0001
	[#]p value vs placebo	<0.0001 (T)		<0.0001 (T)				
Anxiety/ Depression	**Day 0**	2.21 (0.72)	(2.01, 2.41)	2.23 (0.79)	(2.00, 2.46)	2.53 (0.87)	(2.29, 2.77)	[a]0.0803
	Day 30	1.83 (0.79)	(1.61, 2.05)	1.96 (0.81)	(1.72, 2.19)	2.38 (0.84)	(2.15, 2.61)	[a]0.0018
	Change from baseline at day 30	−0.38 (0.63)	(−0.56, −0.21)	−0.28 (0.71)	(−0.49, −0.07)	−0.15 (0.69)	(−0.34, 0.04)	[b]0.0205
	[#]p value vs placebo	0.0116		0.1316				
	Day 90	1.31 (0.58)	(1.15, 1.47)	1.38 (0.64)	(1.19, 1.57)	2.36 (0.94)	(2.10, 2.62)	[a]<0.0001
	Change from baseline at day 90	−0.90 (0.75)	(−1.11, −0.70)	−0.85 (0.66)	(−1.04, −0.66)	−0.17 (0.83)	(−0.40, 0.06)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				
EQ VAS	**Day 0**	63.37 (17.11)	(58.60, 68.13)	64.15 (13.96)	(60.05, 68.25)	60.66 (14.71)	(56.61, 64.71)	[a]0.4861
	Day 30	61.15 (12.74)	(57.61, 64.70)	62.87 (13.46)	(58.92, 66.83)	55.47 (13.35)	(51.79, 59.15)	[a]0.0138
	Change from baseline at day 30	−2.21 (15.13)	(−6.42, 2.00)	−1.28 (14.72)	(−5.60, 3.05)	−5.19 (15.63)	(−9.50, −0.88)	b0.0290
	[#]p value vs placebo	0.0852		0.0226				
	Day 90	77.12 (11.81)	(73.83, 80.40)	72.66 (11.65)	(69.24, 76.08)	52.55 (15.49)	(48.28, 56.82)	[a]<0.0001
	Change from baseline at day 90	13.75 (15.62)	(9.40, 18.10)	8.51 (16.08)	(3.79, 13.23)	−8.11 (17.24)	(−12.87, −3.36)	[b]<0.0001
	[#]p value vs placebo	<0.0001		<0.0001				

Notes: [a]p-values were calculated using ANOVA Test (A). [b]p-values were calculated using Analysis of Covariance (ANCOVA) with treatment as factor and baseline as covariate. [#]p-values were calculated by comparing each treatment group to the placebo group using Dunnett's *T*-test with ANCOVA.
Abbreviations: CI, Confidence interval; N, Number of participants; SD, Standard deviation.

reduced joint pain as assessed by VAS in healthy volunteers.[23] Another study further concluded that the intake of E-PR-01 (400 mg/day) showed a notable reduction of approximately 47% in functional disability as evaluated by the Roland-Morris Questionnaire (RMQ).[24] In line with these findings, in the current study, E-PR-01 HD and LD groups showed clinically meaningful increases of 58.18% and 42.60%, respectively, in the MSK-HQ scores at 90 days. The aforementioned findings collectively indicate a positive impact of E-PR-01 on musculoskeletal health observed in this study. In contrast, the placebo group exhibited a mere 8.25% increase in the scores. Thus, the E-PR-01 proved to be efficacious in achieving a clinically and statistically significant result. In addition to this, the E-PR-01 HD and LD groups also displayed statistically significant reductions in the P-NRS scores at the end of the study. A clinically meaningful reduction of pain is defined as a 2-point decrease or a 30% reduction from baseline.[31] A previous study that used exercise-induced muscle soreness or discomfort concluded that the consumption of ginger led to a reduction in pain as assessed by pain VAS scores.[34] In the current study, by day 90, clinically important results were obtained in the E-PR-01 HD and LD groups exhibiting a percentage reduction of 44.19% and 33.69%, respectively in pain score parameters, whereas, the placebo group had a comparatively lesser percentage reduction of only 10.76%. Similar results were demonstrated in a previous study of E-PR-01 wherein 30 days' supplementation elicited a significant improvement in the low back pain VAS in the E-PR-01 group (41.8%) as opposed to placebo (19.73%).[24] These observations imply that both E-PR-01 HD and E-PR-01 LD reduced discomfort in the index joint when compared to the placebo. This appears to be attributed to the ameliorative effects of ginger on muscular discomfort, which may be the result of reduced production of prostanoids and leukotrienes.[35] Several studies have reported the potential anti-inflammatory and anti-rheumatic activities of ginger in addressing musculoskeletal pain.[18] However, E-PR-01 serves as a unique combination of *V. negundo* and *Z. officinale* that not only helps ease chronic musculoskeletal discomforts but also appears to be efficacious at 200 mg for relieving exercise-induced joint discomfort in physically active individuals. This reduction in the discomfort and improvement in the musculoskeletal health of individuals was also evident by examining the rescue medication usage (E-PR-01 HD and LD lower use than placebo; p=0.0138).

Significant improvements in the ROM for joint flexion are key to better mobility. Twenty-four weeks of administration of undenatured collagen demonstrated a statistically significant 3.23° increase in knee ROM flexion as compared to the placebo.[12] A similar effect of 3.93° was observed in the 12 weeks of administration of the low dose E-PR-01 group whereas the high dose was found to be increasing the active flexion by 4.84°. This effect on the range of motion can be attributed to the structural and functional changes in the assessed index joint. A previous study conducted by Black CD et al reported that both ginger and placebo resulted in a decrease of 1.9% in elbow ROM.[34] Various clinical studies have demonstrated the positive impact on the quality of life on the consumption of *Zingiber officinale* owing to its ability to decrease joint discomfort.[12,35–38] A previous study also reported that intake of E-PR-01 demonstrated significant improvement in work productivity in terms of reduction in - absenteeism, impairment while working and impairment in day-to-day activities in the adult population.[24] Similarly in the current study, there were consistent and significant improvements in the quality of life across all dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of the EQ-5D-5L questionnaire in both E-PR-01 groups compared to placebo over 90 days. Additionally, it was both the low-dose and high-dose groups of the E-PR-01 that successfully achieved a clinically meaningful change by reaching the MCID threshold of 7.5 for EQ-VAS.[39] This improvement indicates a promising therapeutic option for enhancing the overall quality of life for those with joint or low-back discomfort. However, the present study encompassed the limitation of not including individuals with severe joint discomfort conditions. Also, only the knee and low back joints were targeted in the study as individuals with severe joint discomfort might require medical intervention. Non-steroidal anti-inflammatory drugs, the most commonly used analgesics, are known to induce tolerance and lead to habituation on repeated administration.[40] Nevertheless, it was observed in the current study that a prolonged use of the E-PR-01 product resulted in an incremental discomfort relief, thereby signifying no habituation effect of any of the doses used.

Conclusion

The study concluded that E-PR-01 at the dose of 200 and 400 mg per day is effective in improving musculoskeletal health in the population tested. Moreover, the previously explored analgesic effect was reaffirmed in this study at a lower

dose. However, the change in musculoskeletal health was highly dependent on the dose administered and the effect size for all the outcomes was higher in the 400 mg dose. This study adds to the dataset regarding dietary and lifestyle changes that can be utilized for improving perceptive discomfort or pain issues, especially surrounding lower back and joints. The product in line with previous studies has proven to be a promising alternative for enhancing joint flexibility as well as mobility and thereby improving the quality of life. E-PR-01 was found to be safe and well-tolerated.

Data Sharing Statement

The data presented in the study is available on reasonable request from the corresponding author with due permission from the sponsor.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Shalini Srivastava is affiliated with Vedic Lifesciences. The authors declare no conflict of interest.

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