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Original Research Article

Screening of herbal extracts for rapid effect on activity-induced knee joint discomfort: a randomized and placebo-controlled pilot study

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ABSTRACT

Background: A feasibility study was conducted to investigate the effect of different proprietary extracts on joint discomfort associated with repeated episodes of physical activity.
Methods: A single-dose randomized, double-blind, placebo-controlled cross-over study was conducted in three phases with different extract combinations. Seventeen individuals aged 40-60 years with a history of knee joint pain aggravation on physical stress were randomized to receive the investigational product or the placebo in a 1:1 ratio. The primary outcome was the time taken to achieve meaningful pain relief (MPR) from baseline using a pain visual analog scale (VAS) compared to the placebo. The secondary outcomes were the pain intensity difference (PID) and joint discomfort at 1-, 2-, 3-, and 4-hours post-product administration and the time-weighted sum of pain intensity difference (SPID) over 4 hours compared to placebo.
Results: Participants in two out of eight investigational product groups achieved MPR successfully. The proprietary combination ZV-E (consisting of *Z. officinale* and *V. negundo*) showed the fastest pain reduction with more than 50% of the participants achieving meaningful relief. The BS-ZP (consisting of *B. serrata* + *Z. officinale* + *P. lanceolata*) group also had more than 50% of participants reporting MPR at 4 hours post-IP administration. Subsequently, the SPID was found to be lowest in the participants of above stated groups.
Conclusions: The proprietary combination of *Z. officinale* and *V. negundo* extracts, 200 mg could be a promising lead to conduct a further trial to investigate its effect on joint pain.

Keywords: *Zingiber officinale*, *Vitex negundo*, Joint discomfort, Acute pain, MPR, Physical activity

INTRODUCTION

At the advent of a new year, millions of people across the globe resolve to lead a healthy lifestyle and include exercise in their daily routine; however, many of them are forced to give up on this resolution within a few days of starting due to joint pain and fear of overuse injuries. Moreover, the condition worsens with growing age as chondrocytes tend to have low reactivity to growth factors with age leading to altered structure and decreased functional ability in collagen to accommodate exercise-related stress. Common modalities to address such early-stage problems include anti-inflammatory drugs because of their attributes like the quick onset of action, convenient dose, dosage forms, and over-the-counter availability. However, their frequent consumption comes with numerous severe, potentially life-threatening adverse drug reactions like heart attacks or strokes.[1,2] This situation has created an urgent need for a safer and faster alternative for joint pain relief associated with physical activity. In this pursuit, we initiated a feasibility study to investigate the effect of promising leads like *Zingiber officinale*, *Vitex negundo*, *Pluchea lanceolata*, *Boswellia serrata*, *Psidium guajava*, and *Kaempferia*

parviflora on activity-induced knee joint pain and discomfort in otherwise healthy individuals.

Clinical studies have supported the efficacy of phytopharmaceuticals in managing joint pain and discomfort.[3,4,5] In addition, numerous plant-based compounds have demonstrated their activity on different inflammatory pathways[4] and, thus, may prove to be a promising lead in the supportive care of inflammatory disorders, including arthritis.[6] One of the most common conditions in the United States for which adults use complementary and alternative medicine is pain.[7] Ginger rhizome is a well-known Asian spice and an ingredient with a rich history of use as an anti-inflammatory and analgesic agent.[8] It exerts analgesic effects by several pathways which includes but is not limited to COX (cyclooxygenase), LOX (lipoxygenases) and prostaglandin synthesis inhibition, antioxidant activity, inhibition of several cytokines and vanilloid nociceptor competitive agonism.[9,10] Several clinical studies have been conducted to investigate the effect of ginger on exercise-induced pain, muscle soreness and inflammation.[11,12,13] A study conducted in exercising adults demonstrated acute analgesic effect of ginger wherein the daily intake of raw and heat-treated ginger exerted a significant pain reduction in exercise-induced muscle injury.[14] A recent review of clinical trials of ginger concluded that the use of ginger for its pain-lowering effect is safe and promising.[10]

V. negundo has been documented as a potent anti-inflammatory and analgesic ingredient in Ayurveda, supported by several preclinical studies.[8] The bioactive constituents of *V. negundo* comprise volatile oils, flavonoids, lignans, iridoids, terpenes (triterpenes, diterpenes, sesquiterpenes), and steroids.[15] Its pain-suppressing activity is mediated via PG synthesis inhibition, antihistamine, membrane-stabilizing, and antioxidant activities.[16,17]

P. lanceolata is also a traditional herb and an essential ingredient of several polyherbal formulations recommended in ayurvedic treatise for local and systemic administration in the treatment of arthritis. Several clinical studies support the anti-inflammatory and anti-arthritic properties of *B. serrata* extract. In addition, it has demonstrated a good safety profile which enlists it as a promising alternative to NSAIDs.[18] Likewise, *P. guajava* has also shown beneficial effects in managing arthritic disorders in relieving pain and improving joint function.[19,20] *K. parviflora*, also known as "Thai ginseng," has been used in traditional Thai medicine to treat gout, aphthous ulcer, abscesses, allergy, and gastrointestinal disorders.[21]

We conducted a randomized, placebo-controlled, double-blind cross-over feasibility study to explore the effect of the above-mentioned herbal extracts for their analgesic/anti-nociceptive potential in alleviating activity-induced acute joint discomfort compared to placebo.

METHODS

Study design

The present study was designed as a randomized, placebo-controlled, double-blind, single-dose cross-over trial to screen some proprietary herbal extracts for their effect on knee joint pain and discomfort. The study was conducted in three consecutive stages-stage I, stage II, and stage III with a different group of investigational products (IPs), as described in Table 1. It was conducted from August 2020 to April 2021 at Skin Cure N Care, Mumbai, Maharashtra, India.

Table 1: Details of IPs.

Research code	Composition	Dose (mg)	Regimen
Placebo	Microcrystalline cellulose	500	One capsule stat
PL-L	*Pluchea lanceolata* leaf	300	
PL-H	*Pluchea lanceolata* leaf	600	
BS-ZP	*Boswellia serrata* + *Zingiber officinale* rhizome + *Pluchea lanceolata* leaf	400	
PL-Z	*Zingiber officinale* rhizome + *Pluchea lanceolata* leaf	250	
ZP	*Zingiber officinale* rhizome + *Psidium guajava* leaf	400	
ZV-E	*Vitex negundo* leaf + *Zingiber officinale* rhizome	200	
KV	*Kaempferia parviflora* rhizome + *Vitex negundo* leaf	400	

The participants were crossed over for each IP within each phase after a washout period of 7 days, as per the randomization chart generated. New participants were recruited for each consecutive phase of the study. The primary efficacy outcome was time taken to achieve MPR by double stopwatch method, indicated by at least 30 points reduction in pain intensity from baseline on the pain VAS compared to placebo. The secondary outcomes were-a) the PID and joint discomfort at 1-, 2-, 3-, and 4-hours post-IP administration from the baseline as measured on pain and joint discomfort VAS scores and b) the time-weighted SPID 0-4 h, compared to placebo. The study was conducted under the supervision of a qualified medical professional. The participant and the investigator were both blinded to the IP allocation. The randomization sequence was generated by an independent researcher

who was not involved directly in the study. The IP, placebo, and active comparator were matched in color, shape, size, and packaging to preserve the blinding.

Participants

This study complied with the Declaration of Helsinki, International Conference on Harmonization-Good Clinical Practices (ICH-GCP), applicable regulatory guidelines, and Ethical guidelines for Biomedical Research on Human Participants 2006, issued by the Indian Council of Medical Research (ICMR), India. The study was approved by Aditya College of Engineering and Advance Studies (ACEAS)-Independent Ethics Committee, Ahmedabad, Gujarat, India (Reg. No. ECR/281/Indt/GJ/ 2017). The investigator explained the objective, procedures, risks, and benefits involved in the study to all the participants. Written consent was obtained from all the participants before recruitment into the study.

The study included male and female individuals aged 40-60 years with a history of knee joint pain aggravation by physical stress (walking, running, and cycling). The inclusion criteria for pain intensity was-a) ≥ 60 mm self-reported joint pain on a 100 mm VAS scale after walking as per modified Naughton protocol that should not subside within 1 hour of placebo administration after completion of the walking protocol as defined by a pain VAS score of ≥20 mm, and b) no or minimal pain at rest (≤30 mm on VAS scale).[22] The individuals with a BMI within the range of > l8.5 and <29.9 kg/m^2, willing to conform to all the study requirements and give voluntary, written informed consent for participation, were recruited in the study. Female individuals who had ongoing menstruation were rescreened, and their visit was rescheduled after the end of the menstrual period.

Individuals qualifying for osteoarthritis as per American College of Rheumatology (ACR) criteria as well as known cases of osteo-, rheumatic- or any other form of arthritis were excluded from the study. Also, participants with the history or presence of insomnia, restless leg syndrome, uncontrolled hypertension, type II diabetes mellitus, clinically significant renal, hepatic, endocrine, biliary gastrointestinal, pancreatic, or neurological disorders were excluded.

Intervention

The details of the phase-wise interventions are provided in Table 1. The participants were administered the IP on the site after performing baseline assessments. The post-dose efficacy assessments were done at 1, 2, 3, and 4 hours after IP administration.

Study procedures

The participants were pre-screened from a database of healthy individuals based on their age. The pre-screened participants were contacted and informed about the purpose of the study. The individuals who expressed their willingness to participate in the study were invited to the study site for screening as per the eligibility criteria defined for the study. They were instructed to come to the study site in the morning after overnight fasting of at least 12 hours. On the screening visit, after completion of the consent process, medical and medication history, anthropometry, clinical examination, vitals (blood pressure and pulse rate), and fasting blood glucose assessment were performed. In addition, the participants were assessed for the intensity of joint pain on pain VAS at rest and after 10 minutes of walking. Symptoms like pain and discomfort are highly subjective and can be easily influenced by external factors; therefore, the participants were given one dose of placebo and instructed to walk for 2-3 minutes, 1-hour, and 4-hour post-dose to exclude placebo responders (decrease in pain >20 mm on pain VAS). Finally, an anteroposterior X-ray of the participant was performed for KL grading of any osteoarthritic changes in the index joint. The participants who fulfilled all the eligibility criteria were randomly assigned to the study arms as per the pre-generated randomization sequence.

On the IP administration day, the eligible participants visited study site in the morning. All instructions for the protocol were provided clearly to the participants. The participants after an initial resting time of 10 minutes, were examined by the study physician and were subsequently asked to perform 10 minutes-graded physical test (using modified Naughton protocol for-exercise-testing) on the treadmill.[23] Following this, the participants marked their pain intensity on 100-mm visual analogue scale (VAS). The participants were administered the IP after the test and rested until the next treadmill test. The modified Naughton exercise testing protocol was performed at 1, 2, 3 and 4 hours after IP administration. Following each exercise, participants rated their pain on VAS.

A “double stopwatch method” was used to determine the first perceived pain relief (reduction in VAS pain by 100 mm, as perceived by the participants compared with the recently scored baseline) and time taken to achieve MPR (decrease in VAS pain by 30 mm, as perceived by the participants compared with the recently achieved baseline), thus defining the precise onset of the action. Immediately after dosing, the participants were given two stopwatches and instructed that once they started perceiving the pain relief for the first time, they switched off one of the two stopwatches and handed it to the study coordinator.

Similarly, when they experienced MPR, they switched off the second stopwatch. The study coordinator recorded both time points for pain relief. After 1-hour post-IP administration, the participant was again exposed to the same exercise protocol and administered joint and discomfort VAS. The same procedure was repeated at an hourly frequency up to 4 hours post-IP administration.

RESULTS

Participant disposition

A total of 26 participants were screened, of which 19 were eligible for randomization. Two participants were considered randomization failure. Finally, 17 participants were randomized to receive study products (Figure 1).

Demographics and baseline characteristics

The eligible participants for the feasibility study were aged between 40-54 years with 53% males and 47% females. The average BMI of the participants was 25.69 kg/m^2. In addition, all the participants had normal mean blood pressure, pulse rate, and fasting blood glucose (Table 2).

Furthermore, most participants did not have any big osteophytes with joint space narrowing or bony deformation of the affected knee joint (Table 3).

Time taken to achieve MPR

MPR, as defined by a reduction of 30 mm on the 100-mm pain VAS scale, was successfully achieved in more than one participant in two out of eight of the IP groups, as shown in Table 4. The highest number of participants (80%) in the ZV-E group could achieve MPR, which was followed by BS-ZP (75%). On the other hand, in KV and PL-Z groups, only 40% and 14.29% of participants experienced MPR, respectively. All the participants in other groups namely ZP, PL-L, PL-H, and Placebo groups failed to achieve MPR (Table 4 and Figure 2).

The lowest time taken to achieve MPR was observed in the PL-Z group (139.3 minutes); however, only one participant out of seven reported MPR. It was followed consecutively by ZV-E, BS-ZP, and KV (Table 5 and Figure 2).

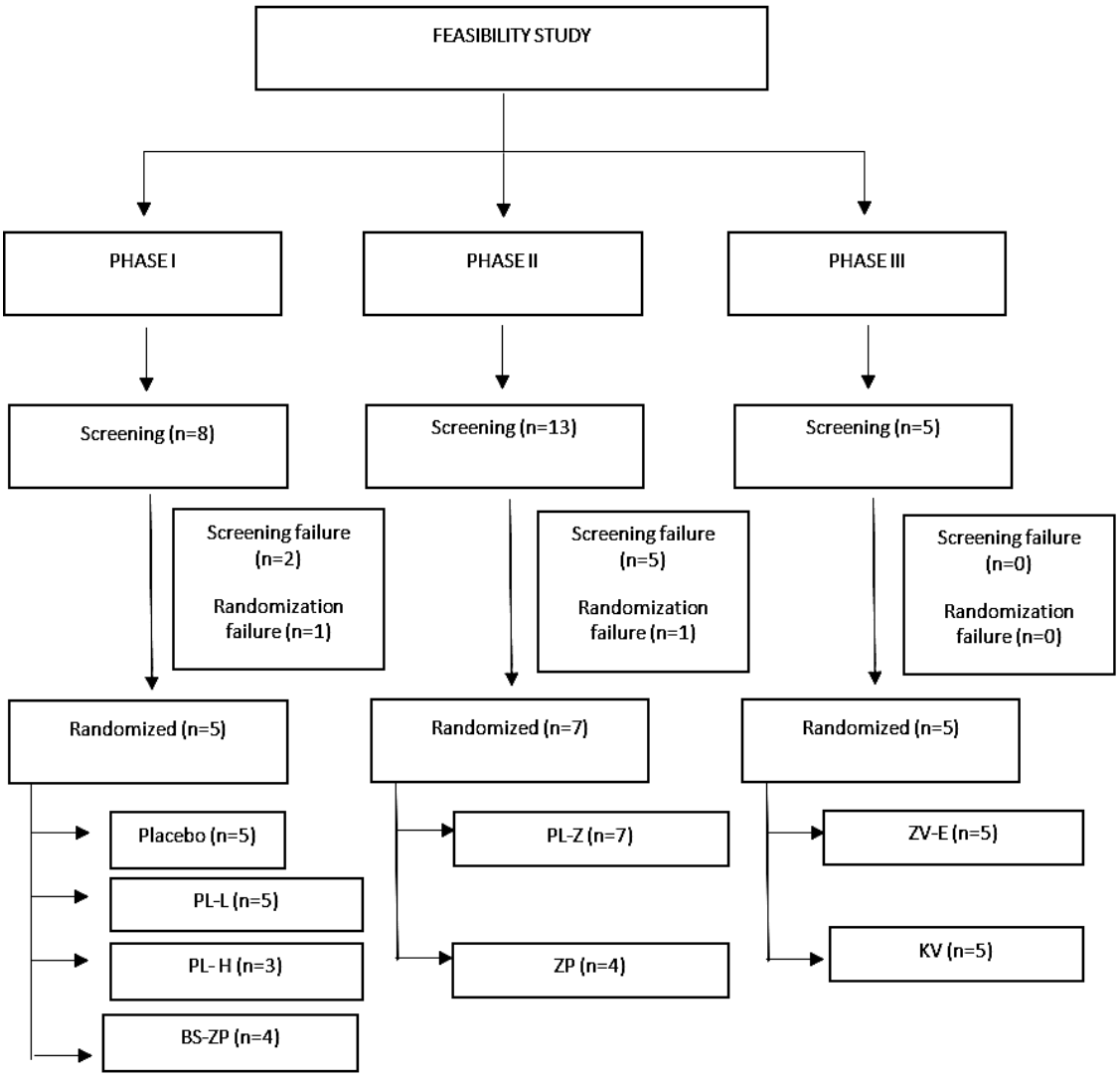

Figure 1: Participant disposition.

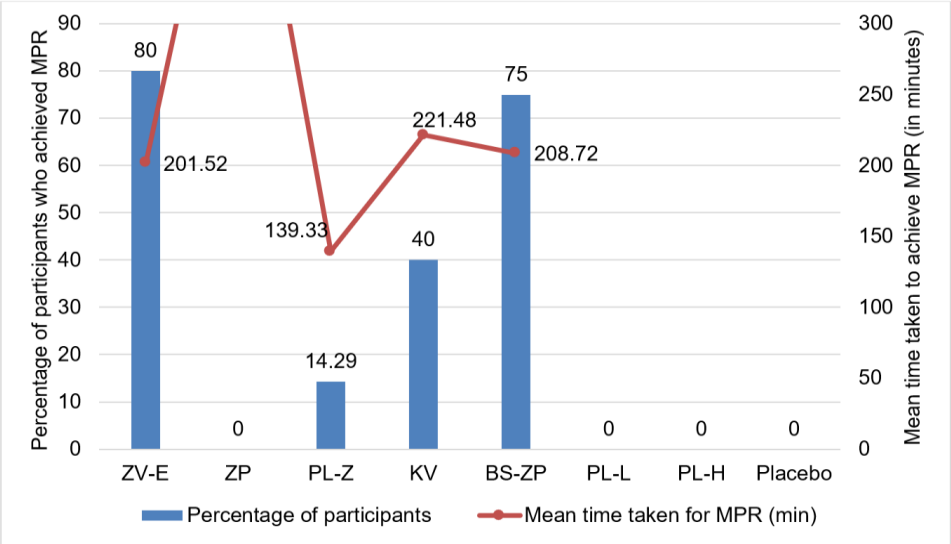

Figure 2: Percentage of participants with MPR and time taken to achieve MPR.

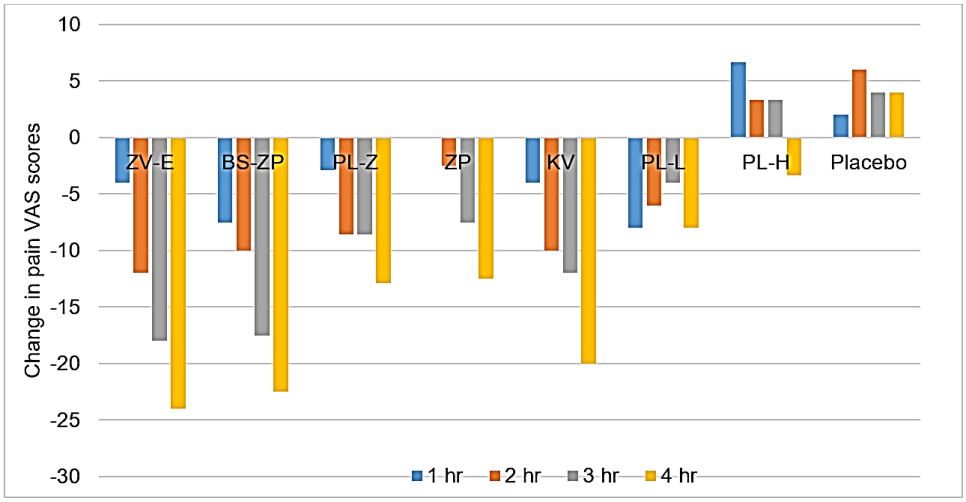

Figure 3: Change in VAS score.

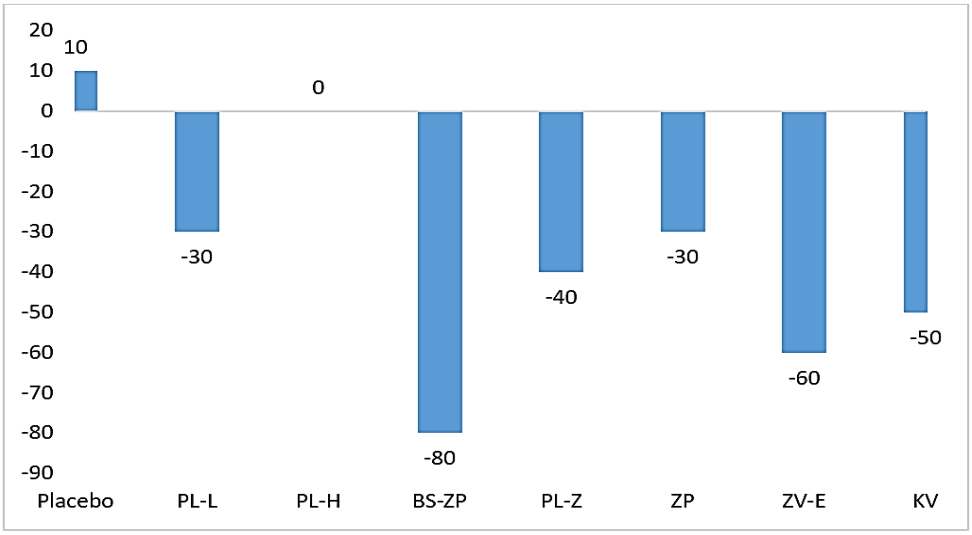

Figure 4: Time-weighted sum of pain intensity difference (mm).

Table 2: Demographics and baseline characteristics.

Characteristics	Mean	SD	95% CI		Min.	Max.
Phase I, (n=5)						
Age (In years)	43.20	1.92	40.81	45.59	40	45
Height (m)	1.62	0.10	1.50	1.74	1.53	1.77
Weight (kg)	68.72	8.22	58.51	78.93	60.3	80
BMI (kg/m^2)	26.06	2.29	23.22	28.91	23.56	28.69
PR (beats/min.)	79.40	5.08	73.09	85.71	73	86
SBP (mm Hg)	123.80	3.35	119.64	127.96	120	128
DBP (mm Hg)	82.00	3.94	77.11	86.89	76	86
FBG (mg/dL)	90.84	1.06	89.52	92.16	90	92
Phase II, (n=7)						
Age (In years)	48.57	3.74	45.12	52.03	46	54
Height (m)	1.64	0.07	1.58	1.71	1.54	1.73
Weight (kg)	70.21	9.14	61.76	78.67	61.2	85
BMI (kg/m^2)	25.89	1.79	24.23	27.54	23.32	28.40
PR (beats/min.)	76.86	6.01	71.30	82.42	68	86
SBP (mm Hg)	127.14	9.58	118.28	136.00	110	138
DBP (mm Hg)	83.14	3.98	79.47	86.82	80	88
FBG (mg/dL)	100.14	4.30	96.17	104.12	93	105
Phase III, (n=5)						
Age (In years)	48.00	5.70	40.92	55.08	40	54
Height (m)	1.59	0.07	1.50	1.68	1.52	1.7
Weight (kg)	64.84	5.89	57.53	72.15	60	74
BMI (kg/m^2)	25.72	1.58	23.76	27.68	23.32	27.74
PR (beats/min.)	77.80	3.42	73.55	82.05	73	82
SBP (mm Hg)	123.40	9.99	111.00	135.80	110	136
DBP (mm Hg)	81.40	2.19	78.68	84.12	80	85
FBG (mg/dL)	97.60	5.86	90.33	104.87	92	106

BMI=body mass index; CI=confidence interval; DBP=diastolic blood pressure; FBG=fasting blood glucose; Max=maximum; Min=minimum; n=number of participants; PR=pulse rate; SBP=systolic blood pressure; SD=standard deviation.

Table 3: Sex and KL grade distribution.

Variables	Phase I	Phase II	Phase III	Total
Sex				
Female	3 (60)	3 (42.86)	3 (60)	9 (52.94)
Male	2 (40)	4 (57.14)	2 (40)	8 (47.06)
KL grades				
Grade 0	2 (40)	0	0	2 (11.76)
Grade I	3 (60)	6 (85.71)	5 (100)	14 (82.35)
Grade II	0 (0)	1 (14.29)	0 (0)	1 (5.88)

KL, Kellgren Lawrence; n, number of participants.

Table 4: Number of participants with MPR.

Study group	MPR achieved		MPR not achieved		Total
	N	%	N	%	
Placebo	0	0	5	100	5
PL-L	0	0	5	100	5
PL-H	0	0	3	100	3
BS-ZP	3	75	1	25	4
PL-Z	1	14.29	6	85.71	7
ZP	0	0	4	100	4
ZV-E	4	80	1	20	5
KV	2	40	3	60	5

Abbreviations: MPR, meaningful pain relief; n, number of participants.

Table 5: Time taken to achieve MPR (minutes).

Study groups	N	Mean	SD	95% CI		Min.	p25	p75	Max.
Placebo	5								
PL-L	5	MPR not achieved							
PL-H	3								
BS-ZP	4	208.72	44.89	97.22	320.23	170.2	170.17	258	258
PL-Z	7	139.33	.	.	.	139.3	139.33	139.33	139
ZP	4	MPR not achieved							
ZV-E	5	201.52	31.24	151.81	251.22	155.2	182.79	220.24	220
KV	5	221.48	22.43	19.98	422.97	205.6	205.62	237.33	237

Table 6: Pre- and post-exertion VAS scores (mm).

Time-points	Pre-exertion						Post-exertion					
	Mean	SD	95% CI		p25	p75	Mean	SD	95% CI		p25	p75
Placebo, (n=5)												
0 hr	20	7.07	11.22	28.78	20	20	70	7.07	61.22	78.78	70	70
1 hr	52	19.24	28.12	75.88	40	60	72	8.37	61.61	82.39	70	80
2 hr	54	15.17	35.17	72.83	40	70	76	5.48	69.2	82.8	70	80
3 hr	56	13.42	39.34	72.66	50	70	74	8.94	62.89	85.11	70	80
4 hr	52	17.89	29.79	74.21	40	70	74	8.94	62.89	85.11	70	80
PL-L, (n=5)												
0 hr	24	5.48	17.2	30.8	20	30	72	4.47	66.45	77.55	70	70
1 hr	50	10	37.58	62.42	40	60	64	5.48	57.2	70.8	60	70
2 hr	50	10	37.58	62.42	40	60	66	8.94	54.89	77.11	60	70
3 hr	50	15.81	30.37	69.63	40	60	68	14.83	49.58	86.42	60	70
4 hr	48	13.04	31.81	64.19	40	60	64	16.73	43.22	84.78	50	70
PL-H, (n=3)												
0 hr	23.33	5.77	8.99	37.68	20	30	66.67	5.77	52.32	81.01	60	70
1 hr	50	17.32	6.97	93.03	30	60	73.33	5.77	58.99	87.68	70	80
2 hr	46.67	23.09	-10.7	104.04	20	60	70	10	45.16	94.84	60	80
3 hr	50	17.32	6.97	93.03	30	60	70	10	45.16	94.84	60	80
4 hr	46.67	15.28	8.72	84.61	30	60	63.33	5.77	48.99	77.68	60	70
BS-ZP, (n=4)												
0 hr	22.5	5	14.54	30.46	20	25	65	5.77	55.81	74.19	60	70
1 hr	32.5	17.08	5.32	59.68	20	45	57.5	5	49.54	65.46	55	60
2 hr	30	14.14	7.5	52.5	20	40	55	10	39.09	70.91	50	60
3 hr	27.5	12.58	7.48	47.52	20	35	47.5	15	23.63	71.37	40	55
4 hr	22.5	9.57	7.27	37.73	15	30	42.5	12.58	22.48	62.52	35	50
PL-Z, (n=7)												
0 hr	24.29	5.35	19.34	29.23	20	30	64.29	5.35	59.34	69.23	60	70
1 hr	28.57	10.69	18.68	38.46	20	30	61.43	12.15	50.19	72.67	50	70
2 hr	30	16.33	14.9	45.1	20	50	55.71	13.97	42.79	68.64	50	70
3 hr	28.57	14.64	15.03	42.11	20	40	55.71	17.18	39.82	71.61	40	70
4 hr	28.57	14.64	15.03	42.11	20	40	51.43	15.74	36.88	65.98	40	70
ZP, (n=4)												
0 hr	22.5	5	14.54	30.46	20	25	62.5	5	54.54	70.46	60	65
1 hr	30	11.55	11.63	48.37	20	40	62.5	5	54.54	70.46	60	65
2 hr	27.5	9.57	12.27	42.73	20	35	60	11.55	41.63	78.37	50	70
3 hr	25	5.77	15.81	34.19	20	30	55	5.77	45.81	64.19	50	60
4 hr	20	8.16	7.01	32.99	15	25	50	8.16	37.01	62.99	45	55
ZV-E, (n=5)												
0 hr	28	4.47	22.45	33.55	30	30	64	5.48	57.2	70.8	60	70
1 hr	34	11.4	19.84	48.16	30	40	60	0	60	60	60	60
2 hr	32	13.04	15.81	48.19	20	40	52	4.47	46.45	57.55	50	50
3 hr	28	16.43	7.6	48.4	20	40	46	8.94	34.89	57.11	40	50
4 hr	28	16.43	7.6	48.4	20	40	40	12.25	24.79	55.21	30	40
KV, (n=5)												
0 hr	26	5.48	19.2	32.8	20	30	62	4.47	56.45	67.55	60	60
1 hr	34	11.4	19.84	48.16	30	40	58	8.37	47.61	68.39	50	60
2 hr	34	11.4	19.84	48.16	30	40	52	13.04	35.81	68.19	40	60
3 hr	32	8.37	21.61	42.39	30	40	50	14.14	32.44	67.56	40	60
4 hr	28	10.95	14.4	41.6	30	30	42	13.04	25.81	58.19	30	50

Table 7: Change in pain VAS scores (mm).

Time-points	Mean	SD	% Change	95% CI		p25	p75
Placebo, (n=5)							
1 hr	2	4.47	2.86	-3.55	7.55	0	0
2 hr	6	5.48	8.57	-0.8	12.8	0	10
3 hr	4	5.48	5.71	-2.8	10.8	0	10
4 hr	4	5.48	5.71	-2.8	10.8	0	10
PL-L, (n=5)							
1 hr	-8	4.47	-11.11	-13.55	-2.45	-10	-10
2 hr	-6	5.48	-8.33	-12.8	0.8	-10	0
3 hr	-4	11.4	-5.56	-18.16	10.16	-10	0
4 hr	-8	13.04	-11.11	-24.19	8.19	-20	0
PL-H, (n=3)							
1 hr	6.67	11.55	9.99	-22.02	35.35	0	20
2 hr	3.33	5.77	4.99	-11.01	17.68	0	10
3 hr	3.33	5.77	4.99	-11.01	17.68	0	10
4 hr	-3.33	5.77	-5.01	-17.68	11.01	-10	0
BS-ZP, (n=4)							
1 hr	-7.5	5	-11.54	-15.46	0.46	-10	-5
2 hr	-10	14.14	-15.38	-32.5	12.5	-20	0
3 hr	-17.5	18.93	-26.92	-47.62	12.62	-30	-5
4 hr	-22.5	15	-34.62	-46.37	1.37	-30	-15
PL-Z, (n=7)							
1 hr	-2.86	9.51	-4.45	-11.65	5.94	-10	0
2 hr	-8.57	12.15	-13.35	-19.81	2.67	-10	0
3 hr	-8.57	15.74	-13.35	-23.12	5.98	-20	0
4 hr	-12.86	13.8	-20	-25.62	-0.09	-20	0
ZP, (n=4)							
1 hr	0	8.16	0	-12.99	12.99	-5	5
2 hr	-2.5	9.57	-4	-17.73	12.73	-10	5
3 hr	-7.5	5	-12	-15.46	0.46	-10	-5
4 hr	-12.5	9.57	-20	-27.73	2.73	-20	-5
ZV-E, (n=5)							
1 hr	-4	5.48	-6.25	-10.8	2.8	-10	0
2 hr	-12	8.37	-18.75	-22.39	-1.61	-20	-10
3 hr	-18	10.95	-28.13	-31.6	-4.4	-20	-20
4 hr	-24	13.42	-37.5	-40.66	-7.34	-30	-30
KV, (n=5)							
1 hr	-4	5.48	-6.45	-10.8	2.8	-10	0
2 hr	-10	10	-16.13	-22.42	2.42	-20	0
3 hr	-12	10.95	-19.35	-25.6	1.6	-20	0
4 hr	-20	10	-32.26	-32.42	-7.58	-30	-10

Table 8: SPID (0-4 hour).

Time-points	Mean	SD	% Change	95% CI		p25	p75
Placebo, (n=5)							
1 hr	2	4.47	2.86	-3.55	7.55	0	0
2 hr	6	5.48	8.57	-0.8	12.8	0	10
3 hr	4	5.48	5.71	-2.8	10.8	0	10
4 hr	4	5.48	5.71	-2.8	10.8	0	10
SPID	16						
PL-L, (n=5)							
1 hr	-8	4.47	-11.11	-13.55	-2.45	-10	-10
2 hr	-6	5.48	-8.33	-12.8	0.8	-10	0
3 hr	-4	11.4	-5.56	-18.16	10.16	-10	0
4 hr	-8	13.04	-11.11	-24.19	8.19	-20	0
SPID	-26						

Continued.

Time-points	Mean	SD	% Change	95% CI		p25	p75
PL-H, (n=3)							
1 hr	6.67	11.55	9.99	-22.02	35.35	0	20
2 hr	3.33	5.77	4.99	-11.01	17.68	0	10
3 hr	3.33	5.77	4.99	-11.01	17.68	0	10
4 hr	-3.33	5.77	-5.01	-17.68	11.01	-10	0
SPID	10						
BS-ZP, (n=4)							
1 hr	-7.5	5	-11.54	-15.46	0.46	-10	-5
2 hr	-10	14.14	-15.38	-32.5	12.5	-20	0
3 hr	-17.5	18.93	-26.92	-47.62	12.62	-30	-5
4 hr	-22.5	15	-34.62	-46.37	1.37	-30	-15
SPID	-57.5						
PL-Z, (n=7)							
1 hr	-2.86	9.51	-4.45	-11.65	5.94	-10	0
2 hr	-8.57	12.15	-13.35	-19.81	2.67	-10	0
3 hr	-8.57	15.74	-13.35	-23.12	5.98	-20	0
4 hr	-12.86	13.8	-20	-25.62	-0.09	-20	0
SPID	-32.8						
ZP, (n=4)							
1 hr	0	8.16	0	-12.99	12.99	-5	5
2 hr	-2.5	9.57	-4	-17.73	12.73	-10	5
3 hr	-7.5	5	-12	-15.46	0.46	-10	-5
4 hr	-12.5	9.57	-20	-27.73	2.73	-20	-5
SPID	-22.5						
ZV-E, (n=5)							
1 hr	-4	5.48	-6.25	-10.8	2.8	-10	0
2 hr	-12	8.37	-18.75	-22.39	-1.61	-20	-10
3 hr	-18	10.95	-28.13	-31.6	-4.4	-20	-20
4 hr	-24	13.42	-37.5	-40.66	-7.34	-30	-30
SPID	-58						
KV, (n=5)							
1 hr	-4	5.48	-6.45	-10.8	2.8	-10	0
2 hr	-10	10	-16.13	-22.42	2.42	-20	0
3 hr	-12	10.95	-19.35	-25.6	1.6	-20	0
4 hr	-20	10	-32.26	-32.42	-7.58	-30	-10
SPID	-46						

CI=confidence interval; n=number of participants; p25, 25th percentile, p75, 75th percentile; SD=standard deviation; SPID=sum of pain intensity difference.

Pain intensity

Table 6 and Figure 3 (research materials file) shows the pre-exercise joint pain and the exacerbation of pain post-exertion by means of VAS scores for all the groups at different time points. Post exertion, 80% participants in ZV-E followed by 75% in BS-ZP, demonstrated a highest clinically meaningful reduction in pain VAS scores, as compared to the baseline. Both the groups had reduction of more than 30% of the pain VAS score. The KV group cumulatively also showed a reduction of more than in the pain VAS score however only 40% of the participants could achieve MPR. The change in the pain VAS score at various time point has been presented in Table 7. In contrast to other groups, the pre-exercise pain remained low in all the three above mentioned groups. Also, the 75th percentile (p75) data indicated that only in the ZV-E group, the post exertion pain score was less than 40 at 4th hour, while in all other groups, this value (p75) was more than 40.

SPID 0-4 hour

The mean time-weighted SPID 0-4 hour of -58 was observed in the ZV-E group followed by -57.5 in BS-ZP and -46 in the KV groups. The remaining groups, i.e., PL-Z, PL-L, ZP also showed a SPID in descending order but less than the above groups. The Placebo and PL-H groups showed increase in the pain intensity with the SPID 16 and 10, respectively (Figure 4 and Table 8).

DISCUSSION

Physical activity significantly reduces morbidity leading to better quality of life. Its benefits extend from cardiovascular health to an individual's musculoskeletal and neurological well-being, specifically for the elderly.

However, activity-induced joint pain limits an individual's physical function and quality of life-whether elderly or a sportsperson. The main extracts used in this proof-of-concept study are *Z. officinale, V. negundo, P. lanceolata, B. serrata, P. guajava, and K. parviflora*. All of these ingredients are well-known for their anti-inflammatory and antinociceptive effect.[10,15,24,25,20] However, no data is available on their rapid analgesic effect.

The study results showed that the *Z. officinale* and *V. negundo* have a clinically significant effect on exercise-induced pain. Out of these combinations, the ZV-E group

with *V. negundo* + *Z. officinale* (200 mg) had the highest number of participants achieving MPR. Also, p75 showed that the decrease in the pain VAS was highest in the ZV-E. Going by the 80/20 rule for degenerative joint pain, with use of a potent analgesic, generally, 80% of patients experiencing 20% pain relief but only 20% experiencing 80% relief and about half have their pain halved.[26]

In case of ZV-E, 80% participants experienced MPR. Hence, we recommend ZV-E, comprising of *V. negundo* and *Z. officinale*, for further confirmatory studies.

Several studies have investigated the efficacy of natural formulations in reducing exercise-induced muscle damage, soreness, and joint pain.[27-30] However, in these studies, the duration of intervention was longer; therefore, these studies cannot be directly compared with the present study.

CONCLUSION

Overall, the study results showed that the combination of *Z. officinale* and *V. negundo* in the specified dose of 200 mg provides clinically MPR in a considerably larger population compared to other groups. This product could serve as a promising lead for further trials for rapid analgesia in musculoskeletal conditions.

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