



Article

Effects of Zembrin[®] (*Sceletium tortuosum*) Supplementation on Mood, Soreness, and Performance Following Unaccustomed Resistance Exercise: A Pilot Study

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Abstract: The purpose of this study was to investigate acute Zembrin[®] (*Sceletium tortuosum*) supplementation on muscle soreness, markers of muscle damage, mood, and exercise performance following unaccustomed resistance exercise. Untrained females ($n = 16$) were divided into two groups with a different three-day treatment regimen: (1) placebo (PL) and (2) Zembrin[®] (ZEM). During the initial visit, baseline perceived soreness, range of motion (ROM), mood state (profile of mood states (POMS) questionnaire), and plasma lactate dehydrogenase concentrations (LDH) were measured followed by the performance of an eccentric bicep curl protocol with their non-dominant arm. The total repetitions and rate of perceived exertion (RPE) were recorded throughout the exercise. The participants then supplemented with the corresponding treatment immediately following, the subsequent day, and 30 min prior to completing a 48 h follow-up visit. For the 48 h visit, all procedures were repeated and comparisons were drawn for perceived soreness, ROM, LDH, mood scores, total repetitions, and RPE. The findings indicate that short-term ZEM supplementation resulted in lower perceived soreness ($p = 0.020$) and a greater preservation of ROM ($p = 0.028$) at 48 h versus the PL group. Mood worsened from the baseline to 48 h regardless of the treatment ($p = 0.043$) but the decrements were exacerbated in the PL group compared with the ZEM group ($p < 0.001$). LDH levels ($p = 0.019$) and RPE ($p = 0.008$) were higher and total repetitions were lower ($p < 0.001$) at 48 h irrespective of the treatment. Although short-term dietary enrichment with ZEM did not alter the exercise performance or biomarkers of muscle damage, the current results suggest ZEM supplementation may be effective in reducing the markers of soreness and preserve mood following unaccustomed eccentric exercise.

Keywords: range of motion; delayed onset muscle soreness; lactate dehydrogenase; profile of mood states

1. Introduction

Sceletium tortuosum (sold as a standardized extract under the name Zembrin[®] (ZEM)) is a succulent plant native to the South African region [1]. In traditional folk medicine, leaves from the plant have been chewed or used in teas and implicated in the amelioration of thirst, staving hunger, and decreasing fatigue [2]. As of late, ZEM has been identified as a promising nutraceutical with potent anxiolytic and anti-depressant actions [3,4]. These actions are likely manifested through high mesembrine alkaloid concentrations within ZEM, which have been reported to alter central nervous system activity [5]. High levels of anxiety and negative effects have been suggested to induce hyperalgesia during and after exercise as well as diminishing exercise performance [6,7]. Thus, identifying therapeutic strategies to combat anxiety and mood disturbances during and after intense exercise are

needed for training and competition in efforts to achieve peak performance. However, the effects of ZEM on exercise performance and soreness remain largely unclear.

Although the physiological mechanisms for the anxiolytic and mood-enhancing actions of ZEM have not been fully elucidated, multiple studies have reported underpinning mechanisms to be the inhibition of phosphodiesterase-4 (PDE-4) and the blockade of 5-hydroxytryptamine (5HT) reuptake [3,8]. Previous investigations have shown that PDE-4 inhibition results in increased cyclic-adenosine monophosphate (cAMP) signaling in neural tissue, thereby increasing cellular signal transduction [9,10]. Bolstering this, psychological disorders, such as depression, have been shown to have diminished neuronal cAMP signaling [11]. ZEM has been shown by multiple groups to be a strong PDE-4 inhibitor [8,12]. For example, Harvey et al. reported that ZEM potently inhibited human myeloid cell-derived PDE-4 activity [8]. 5HT reuptake and transport has also been shown to be blunted by ZEM treatment [8,13]. Coetzee et al. showed that mesembrine alkaloids, derived from *Sceletium tortuosum*, resulted in a reduced 5HT transporter protein expression in human astrocyte and murine hippocampal cells [13]. Of particular importance, 5HT reuptake inhibitors are commonly used in the pharmacological treatment of anxiety and mood disorders [14]. Moreover, the synergistic ablation of 5HT reuptake and PDE-4 activity may provide a greater relief of depressive symptoms, suggesting that the actions of ZEM may be optimized through a pleiotropic neuromodulation [15]. Reports of analgesic and anti-inflammatory actions have also been reported with ZEM treatment [16]. Bennet et al. showed *Sceletium tortuosum* extracts blunt cytokine release and may protect against low levels of systemic inflammation [16]. Furthermore, rodents treated with alkaloids from ZEM showed decreased nociceptive pain responses similar to opioid compounds, indicating a strong analgesic efficacy from ZEM [17]. Altogether, ZEM appears to be an effective nutraceutical with multi-faceted actions through the modulation of mood, anxiety, pain, and possibly inflammation. However, translational studies to humans are limited, especially in the context of exercise, leaving the need for further study.

Investigations of ZEM treatment in humans have been primarily studied in the context of anxiety and mood [3,4,18]. Terburg et al. showed that ZEM treatment decreased anxiety-related amygdala activation and may diminish threat responsivity by amygdala-hypothalamus decoupling [3]. Improvements in mood and sleep patterns, and reductions in anxiety, have also been reported in young healthy adults [4,18]. We are only aware of one investigation studying how ZEM supplementation influences responses to physical exercise. Recently, Hoffman et al. demonstrated that 8 days of ZEM supplementation improved the complex reaction time and physical task performance with a high cognitive load [19]. However, mood was minimally affected (albeit all participants were young and healthy) and no stimulus was provided to alter the emotional state. Studies from our lab and others have suggested a role for anxiety and negative effects on the exacerbation of pain and soreness, and reductions in subsequent performance following intense exercise [20,21]. As the maintenance of mood and exercise performance are important in optimizing long-term training and athletic performance [22], identifying natural remedies that may serve as a panacea for underlying negative symptoms after intense exercise is highly desirable. To date, no investigations have studied how ZEM may influence soreness and performance following intense exercise. Thus, the purpose of this study was to provide a preliminary investigation into the effects of acute ZEM (*Sceletium tortuosum*) supplementation on the markers of muscle soreness/damage, mood, and exercise performance following unaccustomed resistance exercise. We hypothesized that ZEM treatment would attenuate muscle soreness/damage and improve mood, thereby preserving exercise performance 48 h after intense eccentric exercise.

2. Materials and Methods

2.1. Study Design

A convenience sample of non-resistance-trained females ($n = 16$) were randomly assigned into one of two groups, (1) Zembrin (ZEM; *Sceletium tortuosum*; $n = 8$) and (2) placebo

(PL; gluten-free cornstarch; $n = 8$), in a double-blinded, between-groups study design. Each participant completed two trials each separated by 48 h. During the first baseline visit, the participants completed baseline perceived soreness, range of motion (ROM), and plasma collection for lactate dehydrogenase measurements. For the subsequent unaccustomed resistance exercise, the participants completed an eccentric bicep curl descending pyramid while the completed repetitions and the rate of perceived exertion (RPE) were recorded. An abbreviated profile of mood state (POMS) questionnaire was also administered before and after exercise. The participants then supplemented with Zembrin or a placebo until the follow-up visit 48 h later. All measurements were then repeated identical to the first baseline visit. Comparisons for all measurements were made between the time points of data collection and treatments.

2.2. Participants

A convenience sample of healthy, non-resistance-trained females ($n = 16$; age = 21.0 year ± 1.6 ; height = 164.0 cm ± 6.1 ; body mass = 64.9 kg ± 15.9) were recruited to participate in this study. Non-resistance-trained was defined as participating in strength training no more than one time per week [20,23]. The exclusion criteria included: upper body injuries within the past six months, a current disease or diagnosis that limited the exercise capacity, a diagnosis with a mood disorder, or a current therapy with anti-depressant or anti-anxiety medication. To screen for the suitability of exercise, each participant completed a physical activity readiness questionnaire (PAR-Q) [23]. Before each visit, the participants were asked to refrain from vigorous activity 24 h prior and from consuming caffeine, nicotine, and alcohol 12 h prior [24]. The participants were asked to maintain their normal sleep and dietary routines prior to each visit.

2.3. Supplementation

The participants underwent a short-term supplementation regimen with either ZEM (Nutricost, N. Vineyard, UT, USA) or PL (gluten-free cornstarch). The participants ingested a single dose of 25 mg/day over three days immediately following exercise on the baseline visit, 24 h post-exercise, and 30 min prior to returning for their 48 h visit [5]. Gluten-free cornstarch was encapsulated in a size “00” gelatin capsule and matched in appearance to the ZEM treatment [20,24]. All treatments were distributed in a double-blinded manner whereby an independent researcher organized non-identifiable opaque bags containing each treatment. To ensure compliance, the empty bags were returned by the participants and recorded. No participants reported any side effects from the supplementation throughout the investigation.

2.4. Muscle Damage Biomarker (Plasma Lactate Dehydrogenase Activity)

Approximately 500–600 μL of capillary blood was collected via a finger prick. Briefly, a 17-gauge 2.0 mm depth disposable blade lancet was used to induce bleeding on the medial end of the fourth finger. Using a gentle massaging technique, blood was collected via a capillary action into lithium-heparin coated microvette[®] tubes (SARSTEDT, Newton, NC, USA). The whole blood was then centrifuged at 10,000 rpm for 10 min. The plasma was decanted and stored at $-80\text{ }^{\circ}\text{C}$ until the biochemical analysis, which was completed following the conclusion of the data collection. The total LDH activity was determined using a commercially available colorimetric plate assay (Elabsience, Houston, TX, USA) [25,26]. All samples were analyzed in duplicate and according to the manufacturer's instructions.

2.5. Procedures

Upon arrival for the first baseline visit, height and weight were recorded. The participants then completed an abbreviated POMS questionnaire to assess their overall mood [27,28]. Following this, the baseline elbow ROM and perceived soreness of the bicep brachii on the non-dominant arm were measured. For ROM, the active flexion and extension were measured while seated using a goniometer (Elite Medical Instruments Inc.,

Anaheim, CA, USA) placed proximally with the head of the humerus and distally with the radial styloid [20]. The participants were instructed to extend and flex their arm as much as possible until the point of subjective discomfort and ROM was calculated by subtracting the degree of extension from flexion [20]. Perceived soreness was obtained using an algometer and pain visual analog scale. A bolster was placed behind the elbow with the arm at full extension and an algometer (Wagner instrument, Greenwich, CT, USA) was pressed (40 N) into the mid-point of the muscle belly of the biceps brachii [20]. During this, the participants then rated their pain on a scale of 1 (no pain) to 10 (worst pain possible). A capillary blood sample was then taken as previously described. Following all baseline measurements, the participants completed a descending eccentric bicep curl pyramid. As previously described by Allen et al. [29], starting at full elbow flexion, the participants lowered a 11.34 kg (25 lb) dumbbell with their non-dominant arm over 3 s to the pace of a metronome set to 60 bpm. After a full elbow extension was reached, the researchers assisted the participant to return the dumbbell to the starting position. The participants completed as many repetitions as possible until volitional fatigue or they could no longer keep pace with the metronome. This was repeated while descending 2.25 kg (5 lb) each set until a total load of 2.25 kg (5 lb) was reached. At the 2.25 kg load, the participants completed as many repetitions as possible until failure or until a total of 10 repetitions were completed. The total repetitions were documented at the end of every set and aggregated for the analysis. The rate of perceived exertion was measured on a 1–10 scale from 1 (very easy) to 10 (so hard they could not continue) after each set and averaged across the sessions for the analysis. Following the exercise protocol, the participants were given specific instructions to avoid any recovery methods. This included taking an oral anti-inflammatory (ibuprofen, acetaminophen), taking any “natural” pain relievers such as Vitamin C or ginger, avoiding the application of any pain relief cream and applying any ice or heat to the sore area as well as massaging or intentionally stretching the sore muscle [20,29,30]. All participants were required to return 48 h after the initial baseline visit and all measurements were repeated, and the outcomes were identically measured.

2.6. Data Analysis

All data were analyzed using Jamovi software (Version 0.9; Sydney, Australia). The normality of all data was confirmed using a Shapiro–Wilk test. The statistical analysis was conducted using a 2×2 (Treatment \times Time) repeated measures ANOVA with a Bonferroni–Holm post-hoc test as warranted. For the significant main effects, an individual mean post-hoc analysis was performed as previously recommended by Wei et al. [31]. The estimates of the effect size for the main effects were calculated using eta squared (η^2) and interpreted as 0.01 = small, 0.06 = medium, and ≥ 0.14 = large [32,33]. If warranted, Cohen’s d effect sizes (d) were calculated between the conditions and interpreted as 0.2 = small, 0.5 = moderate, and 0.8 = large [32,33]. The significance was set at $p \leq 0.05$ a priori. All data are presented as a mean \pm standard deviation (SD).

3. Results

3.1. Perceived Soreness, ROM, and Plasma LDH Levels

The soreness and muscle damage markers are presented in Figure 1. For perceived soreness (1–10 scale; Figure 1a), there was a main effect for time ($p < 0.001$; $\eta^2 = 0.715$) and treatment ($p = 0.011$; $\eta^2 = 0.376$). There was no interaction between time and treatment ($p = 0.171$; $\eta^2 = 0.130$). The post-hoc analysis revealed that perceived soreness was higher from the baseline to 48 h in both the PL ($p < 0.001$; $d = 1.91$) and ZEM ($p = 0.031$; $d = 1.71$) treatments. At 48 h, perceived soreness was lower in the ZEM group compared with the PL group ($p = 0.020$; $d = 1.53$). For ROM (degrees; Figure 1b), there was a main effect for time ($p < 0.001$; $\eta^2 = 0.890$). No significant effects were seen for treatment ($p = 0.139$; $\eta^2 = 0.149$). Furthermore, there was a significant interaction between time and treatment ($p = 0.016$; $\eta^2 = 0.350$). ROM decreased at 48 h for both the PL ($p < 0.001$; $d = 3.14$) and ZEM groups ($p < 0.001$; $d = 2.01$) compared with the baseline. ZEM treatment resulted in a greater ROM

at 48 h compared with the PL group ($p = 0.028$; $d = 1.01$). The analysis of plasma LDH levels ($\mu\text{mol}\cdot\text{mL}^{-1}$; Figure 1c) showed a significant main effect for time ($p < 0.019$; $\eta^2 = 0.149$). No significant main effects were observed for treatment ($p < 0.638$; $\eta^2 = 0.010$) or interaction between time and treatment ($p < 0.721$; $\eta^2 = 0.003$). More specifically, large-sized increases in LDH activity were noted at 48 h in both the PL ($p = 0.039$; $d = 1.03$) and ZEM ($p = 0.011$; $d = 0.81$) groups.

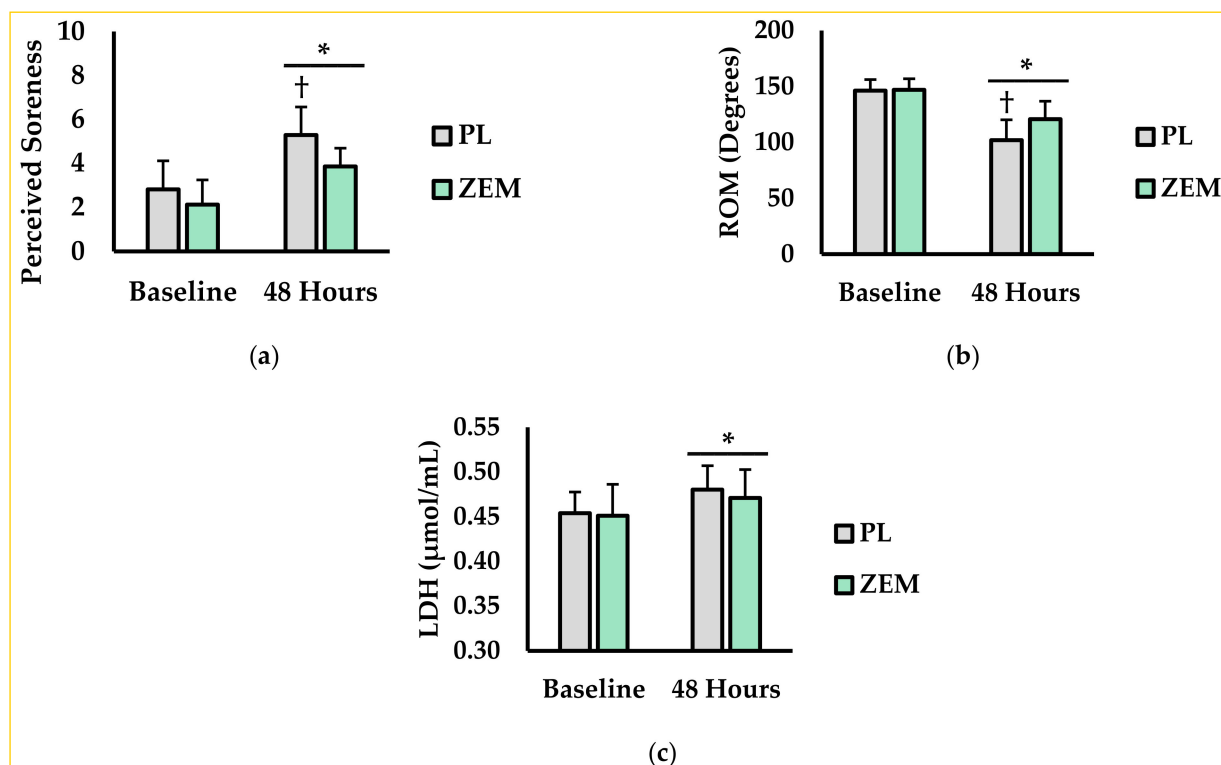


Figure 1. Changes in (a) perceived soreness (1–10 scale), (b) range of motion (ROM; degrees), and (c) plasma lactate dehydrogenase (LDH; $\mu\text{mol}\cdot\text{mL}^{-1}$) from the baseline to 48 h in the placebo (PL) and Zembrin® (ZEM)-treated groups. Data are presented as a mean \pm SD. A statistical analysis was conducted using a 2×2 (Treatment \times Time) repeated measure ANOVA with a Bonferroni–Holm post-hoc test. * indicates a significant difference from the baseline ($p < 0.05$). † indicates a significant difference from ZEM ($p < 0.05$).

3.2. Total Repetitions, RPE, and Mood

For the total repetitions (Figure 2a), there was a main effect for time ($p < 0.001$; $\eta^2 = 0.847$) but not for treatment ($p = 0.683$; $\eta^2 = 0.012$). Moreover, there was no interaction between time and treatment ($p = 0.225$; $\eta^2 = 0.103$). Large decreases in the total repetitions were observed for both the PL ($p < 0.001$; $d = 3.44$) and ZEM ($p < 0.001$; $d = 2.27$) groups. The analysis of RPE, as shown in Figure 2b, showed a significant main effect for time ($p = 0.008$; $\eta^2 = 0.404$) but not for treatment ($p < 0.853$; $\eta^2 = 0.003$). No interaction between time and treatment ($p = 0.177$; $\eta^2 = 0.126$) existed. More specifically, RPE over the session was higher at 48 h compared with the baseline in the PL ($p = 0.039$; $d = 1.27$) but not the ZEM ($p = 0.677$; $d = 0.27$) group. Mood is shown in Figure 2c. There was a significant main effect for time ($p = 0.043$; $\eta^2 = 0.277$) and treatment ($p = 0.029$; $\eta^2 = 0.340$). No significant interaction between time and treatment existed ($p = 0.155$; $\eta^2 = 0.161$). In particular, mood was significantly worse at 48 h compared with the baseline in the PL ($p = 0.032$; $d = 1.76$) but not in the ZEM ($p = 0.647$; $d = 0.54$) group. Additionally, mood was significantly improved in the ZEM group compared with the PL group at 48 h ($p < 0.001$; $d = 1.74$).

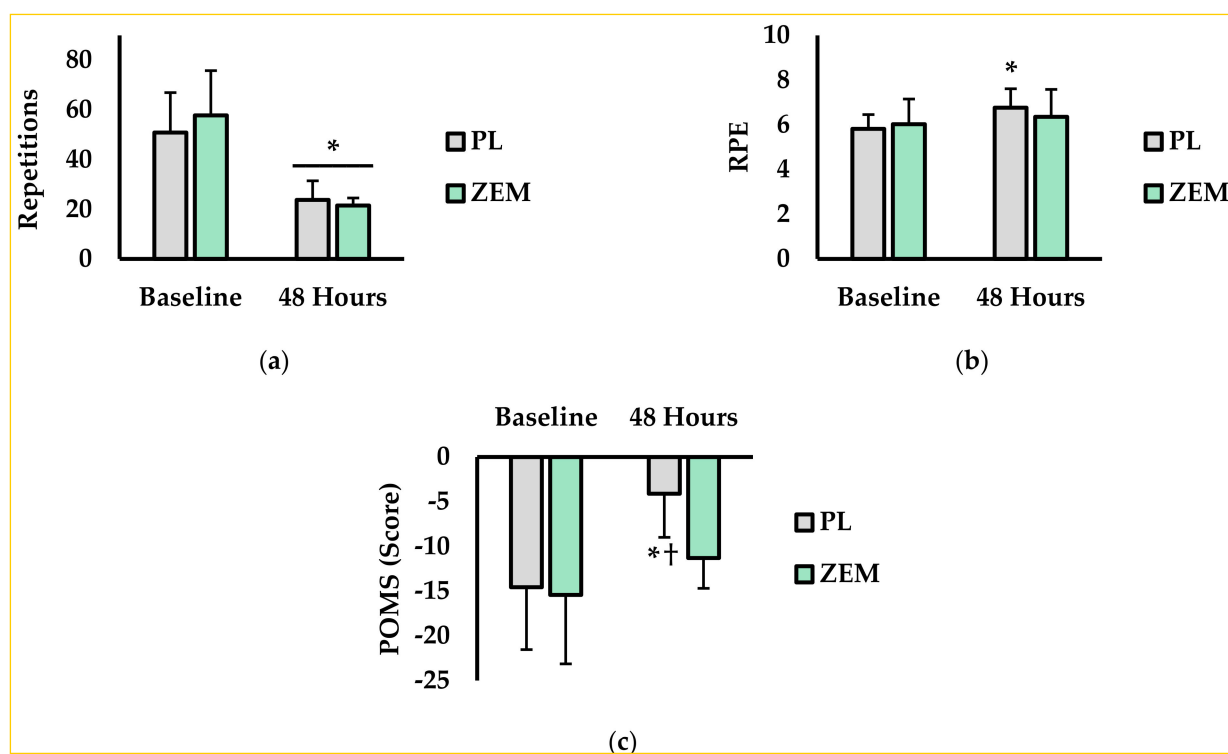


Figure 2. Changes in (a) total repetitions (repetitions), (b) rate of perceived exertion (RPE; 1–10 scale), and (c) profile of mood states (POMS; score) from the baseline to 48 h in the placebo (PL) and Zembrin® (ZEM)-treated groups. Data are presented as a mean \pm SD. A statistical analysis was conducted using a 2×2 (Treatment \times Time) repeated measure ANOVA with a Bonferroni–Holm post-hoc test. * indicates a significant difference from the baseline ($p < 0.05$). † indicates a significant difference from ZEM ($p < 0.05$). Note: a more negative POMS score indicates a better mood.

4. Discussion

ZEM has been widely reported to have anxiolytic, anti-depressant, and mild anti-inflammatory properties [3,4,16]. Although these actions may have the potential to produce favorable outcomes in response to intense exercise, little to no investigations to date have studied the possible interactions of ZEM supplementation, muscle soreness, and performance following unaccustomed intense exercise. Thus, the aim of this study was to elucidate if short-term ZEM supplementation influences muscle damage, soreness, mood, and subsequent exercise performance following intense, unaccustomed resistance exercise. The current findings showed that ZEM decreased perceived soreness and preserved ROM compared with the PL group at 48 h post-exercise, albeit plasma LDH levels were similar regardless of the treatment. ZEM supplementation also resulted in a more favorable overall mood compared with the PL group at 48 h. Although ZEM attenuated increases in RPE at 48 h, both the ZEM and PL groups had a worsened exercise performance. Although the precise physiological mechanisms responsible for the advantageous responses with ZEM cannot be delineated from the present data alone, these preliminary findings may have important implications in using ZEM in recovery following exercise.

Regardless of the treatment, RPE and perceived soreness increased whereas ROM decreased after 48 h, which supports previous findings using the same unaccustomed resistance exercise protocol [20,29]. Unique to the current study, perceived soreness was lower at 48 h with ZEM treatment versus the PL group. Furthermore, RPE was higher at 48 h in the PL group whereas ZEM blunted increases in perceptions of exertion. This is supported by previous studies showing the analgesic effects of ZEM in rodents, albeit the current findings are the first to our knowledge in describing this effect in humans [17]. ROM followed a similar pattern in which both groups had lower ROM after 48 h but ZEM partially attenuated losses in ROM versus the PL group. Although speculative, the benefits

of ZEM supplementation may be due to both physiological and psychological factors. Loria et al. showed similar decreases in pain sensitivity between morphine and ZEM in rats [17]. This dampening in pain responses with ZEM has been previously attributed to the interaction of mesembrine alkaloids with $\delta 2$ - and μ -opioid receptors [8]. Oral opioid treatment has been shown to positively influence musculoskeletal pain and function (i.e., ROM) in older adults, although the effects were small in magnitude [34]. However, it should be noted that a long-term opioid/narcotic use poses considerable health threats to consumers of which the benefits may not outweigh the risks. From a practical standpoint, the current data show that reductions in perceived soreness were large in magnitude, suggesting ZEM could serve as a possible safe and effective alternative in blunting musculoskeletal pain following exercise. Furthermore, the attenuation in increases in RPE may support that ZEM can modulate psychophysiological feelings of discomfort of subsequent exercise. However, the efficacy of ZEM as a pain-altering alternative compared with opioids in humans is completely unknown and further characterization of the analgesic effects in humans is warranted.

Psychological alterations to soreness, RPE, and ROM may have been preserved with ZEM treatment due to decreases in anxiety. Indeed, previous reports in populations similar to the current one have shown potent anxiolytic effects of ZEM treatment [3,4]. High levels of anxiety have been shown to detrimentally affect pain and joint ROM [35,36]. For instance, Kindler et al. showed that anxiety symptoms were associated with joint and muscle hyperalgesia in temporomandibular joint disorders [35]. Furthermore, work from our lab and others have shown that negative expectations and anxiety lead to decreased joint ROM [20,36]. Although not confirmed in the current study, the better outcomes with ZEM may be due to previously reported 5HT reuptake inhibitor mechanisms. 5HT reuptake inhibitors are a cornerstone of psychopharmacological therapy for a wide range of anxiety disorders [37]. This is likely linked to alterations of the emotional state through amygdala activity [3,38]. For example, Terburg et al. demonstrated a lower amygdala reactivity and amygdala-hypothalamus coupling in response to fear and emotional tasks after ZEM treatment [3]. Paired with current findings, it is plausible that ZEM supplementation resulted in reduced anxiety and pain anticipation, ultimately leading to a lower perception of soreness and loss of ROM.

Interestingly, the changes in the perceptive and functional outcomes of soreness were not mirrored by the biomarkers of muscle damage. Plasma LDH increased at 48 h in both groups regardless of the treatment. This suggests that previous reports of the anti-inflammatory effects of ZEM may not have existed currently [16]. Possibly, this may be due to the overall anti-inflammatory effectiveness of ZEM. Bennet et al. suggested that although ZEM has the ability to partially block inflammatory signaling, this may only be beneficial in low-grade inflammation [16]. Thus, muscle damage and inflammation produced by intense exercise in a population unaccustomed to resistance training may overwhelm the capacity of ZEM to exert meaningful anti-inflammatory effects. This may also explain the lack of ergogenic benefits of ZEM. Similar to plasma LDH, there was no treatment effect on the total repetitions and both groups performed worse 48 h later. Given that muscle damage leads to contractile dysfunction [39], ZEM may not have attenuated performance decrements at 48 h due to the inability to prevent tissue damage. However, the reader is cautioned as only an indirect marker of muscle damage was measured, currently necessitating a future study on how ZEM may influence the direct markers of myofiber damage and contractile performance outcomes. Nonetheless, the lack of ergogenic effects currently are supported by previous investigations showing modest to no improvements in simple reaction time and agility [19].

Current data also implicate ZEM as a mood stabilizer. Overall mood was worse at 48 h with the PL treatment whereas ZEM prevented mood disturbance. Furthermore, mood was significantly better at 48 h compared with the PL group. The worse mood in the PL group is supported by previous investigations showing that unaccustomed high intensity exercise results in a poorer mood in athletes [40]. Furthermore, previous descriptions of

ZEM as a 5HT reuptake and PDE-4 inhibitor support the mood stabilization effects as both mechanisms have implications in the treatment for both depression and anxiety [15]. However, our findings are in contrast with a previous work on ZEM and mood during exercise [19]. Hoffman et al. showed that ZEM did not alter mood compared with a PL group after 8 days of supplementation [19]. Although the precise reasons for the disparities between the findings are not fully clear, they may be due to differences in the study design and protocol. Hoffman et al. did not include any stimuli or interventions aimed at altering mood and, thus, there was no mood disturbance for ZEM to counteract. The high intensity unaccustomed exercise in the present study appeared to exacerbate mood disturbances, which may have allowed ZEM to have a greater effect. This is bolstered by previous investigations showing that 5HT reuptake inhibition, one of the primary reported mechanisms of ZEM, improves depressive mood symptoms more effectively in individuals with greater baseline mood disturbances [41]. Thus, ZEM may serve as an effective strategy to combat mood changes following intense exercise or activities where emotional state disturbances are probable.

Although the current study provides novel information on the nutraceutical Zembrin[®], and how it positively affects pain and mood responses following intense exercise, there were several limitations. First, the sample size currently employed was small. As such, these pilot data should be viewed with cautionary optimism with the understanding that future studies with larger and more diverse samples are needed. However, the magnitudes of changes in the outcomes due to ZEM supplementation in the present study were mostly large, which suggests that ZEM has potent effects. All participants in the current investigation were young and healthy. Previous evidence has suggested that ZEM and other agents that alter mood may be more effective in individuals with a disturbance in basal mood [41]. As such, more investigation is needed to determine if a similar benefit is seen in individuals with higher baseline anxiety or mood disorders. Although similar protocols have been described to measure performance [20], only the eccentric exercise repetition volume was currently measured. Typical exercise regimens include the completion of both concentric and eccentric phases of exercise, which may limit the practical application of the present performance data. In conclusion, short-term ZEM treatment results in an attenuation of perceived soreness, a loss of ROM, and an increase in RPE 48 h following unaccustomed resistance exercise. Plasma LDH was unaffected by ZEM treatment as was exercise performance. However, ZEM treatment resulted in the preservation of mood 48 h after intense exercise. These data may prove useful for athletes and competitors looking to combat any ensuing negative psychological effects associated with unaccustomed high intensity exercise.

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Informed Consent Statement: Prior to any data collection, verbal and written informed consent was obtained from each participant. All testing was conducted in our institutional exercise physiology laboratory at Samford University.

Data Availability Statement: Data are contained and available within this manuscript.

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References

1. Gericke, O.; Gericke, N.; Stein, D.J. *Sceletium Tortuosum*; American Psychiatric Association Publishing: Arlington, VA, USA, 2017.
2. Gericke, N.; Viljoen, A.M. Sceletium—A review update. *J. Ethnopharmacol.* **2008**, *119*, 653–663. [\[CrossRef\]](#)
3. Terburg, D.; Syal, S.; Rosenberger, L.A.; Heany, S.; Phillips, N.; Gericke, N.; Stein, D.J.; van Honk, J. Acute effects of Sceletium tortuosum (Zembrin), a dual 5-HT reuptake and PDE4 inhibitor, in the human amygdala and its connection to the hypothalamus. *Neuropsychopharmacology* **2013**, *38*, 2708–2716. [\[CrossRef\]](#)
4. Reay, J.; Wetherell, M.A.; Morton, E.; Lillis, J.; Badmaev, V. Sceletium tortuosum (Zembrin®) ameliorates experimentally induced anxiety in healthy volunteers. *Hum. Psychopharmacol. Clin. Exp.* **2020**, *35*, 1–7. [\[CrossRef\]](#)
5. Dimpfel, W.; Gericke, N.; Suliman, S.; Dipah, G.N.C. Effect of Zembrin® on Brain Electrical Activity in 60 Older Subjects after 6 Weeks of Daily Intake. A Prospective, Randomized, Double-Blind, Placebo-Controlled, 3-Armed Study in a Parallel Design. *World J. Neurosci.* **2016**, *7*, 140–171. [\[CrossRef\]](#)
6. Hardy, L. Stress, anxiety and performance. *J. Sci. Med. Sport* **1999**, *2*, 227–233. [\[CrossRef\]](#)
7. George, S.Z.; Dover, G.C.; Fillingim, R.B. Fear of pain influences outcomes after exercise-induced delayed onset muscle soreness at the shoulder. *Clin. J. Pain* **2007**, *23*, 76–84. [\[CrossRef\]](#)
8. Harvey, A.L.; Young, L.C.; Viljoen, A.M.; Gericke, N.P. Pharmacological actions of the South African medicinal and functional food plant Sceletium tortuosum and its principal alkaloids. *J. Ethnopharmacol.* **2011**, *137*, 1124–1129. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Guo, H.; Cheng, Y.; Wang, C.; Wu, J.; Zou, Z.; Niu, B.; Yu, H.; Wang, H.; Xu, J. FFPM, a PDE4 inhibitor, reverses learning and memory deficits in APP/PS1 transgenic mice via cAMP/PKA/CREB signaling and anti-inflammatory effects. *Neuropharmacology* **2017**, *116*, 260–269. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Hirose, R.; Manabe, H.; Yanagawa, K.; Ohshima, E.; Ichimura, M. Differential effects of PDE4 inhibitors on cortical neurons and T-lymphocytes. *J. Pharmacol. Sci.* **2008**, *106*, 310–317. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Fujita, M.; Richards, E.M.; Niciu, M.J.; Ionescu, D.F.; Zoghbi, S.S.; Hong, J.; Telu, S.; Hines, C.S.; Pike, V.W.; Zarate, C.A. cAMP signaling in brain is decreased in unmedicated depressed patients and increased by treatment with a selective serotonin reuptake inhibitor. *Mol. Psychiatry* **2017**, *22*, 754–759. [\[CrossRef\]](#)
12. Napoletano, M.; Fraire, C.; Santangelo, F.; Moriggi, E. Mesembrine Is an Inhibitor of PDE4 That Follows Structure-Activity Relationship of Rolipram. 2001. Available online: <https://ssrn.com/abstract=2969480> (accessed on 16 September 2021).
13. Coetzee, D.D.; López, V.; Smith, C. High-mesembrine Sceletium extract (Trimesemine™) is a monoamine releasing agent, rather than only a selective serotonin reuptake inhibitor. *J. Ethnopharmacol.* **2016**, *177*, 111–116. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Pringle, A.; Browning, M.; Cowen, P.; Harmer, C. A cognitive neuropsychological model of antidepressant drug action. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2011**, *35*, 1586–1592. [\[CrossRef\]](#)
15. Cashman, J.R.; Voelker, T.; Johnson, R.; Janowsky, A. Stereoselective inhibition of serotonin re-uptake and phosphodiesterase by dual inhibitors as potential agents for depression. *Bioorg. Med. Chem.* **2009**, *17*, 337–343. [\[CrossRef\]](#)
16. Bennett, A.C.; Smith, C. Immunomodulatory effects of Sceletium tortuosum (Trimesemine™) elucidated in vitro: Implications for chronic disease. *J. Ethnopharmacol.* **2018**, *214*, 134–140. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Loria, M.J.; Ali, Z.; Abe, N.; Sufka, K.J.; Khan, I.A. Effects of Sceletium tortuosum in rats. *J. Ethnopharmacol.* **2014**, *155*, 731–735. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Chiu, S.; Gericke, N.; Farina-Woodbury, M.; Badmaev, V.; Raheb, H.; Terpstra, K.; Antongiorgi, I.; Bureau, Y.; Cernovsky, Z.; Hou, J. Proof-of-concept randomized controlled study of cognition effects of the proprietary extract scelletium tortuosum (Zembrin) targeting phosphodiesterase-4 in cognitively healthy subjects: Implications for Alzheimer’s dementia. *Evid.-Based Complement. Altern. Med.* **2014**, *2014*, 682014. [\[CrossRef\]](#)
19. Hoffman, J.R.; Markus, I.; Dubnov-Raz, G.; Gepner, Y. Ergogenic effects of 8 Days of scelletium tortuosum supplementation on mood, visual tracking, and reaction in recreationally trained men and women. *J. Strength Cond. Res.* **2020**, *34*, 2476–2481. [\[CrossRef\]](#)
20. McLemore, B.H.; McLemore, S.G.; Rogers, R.R.; Pederson, J.A.; Williams, T.D.; Marshall, M.R.; Ballmann, C.G. Nocebo Effects on Perceived Muscle Soreness and Exercise Performance Following Unaccustomed Resistance Exercise: A Pilot Study. *J. Funct. Morphol. Kinesiol.* **2020**, *5*, 40. [\[CrossRef\]](#)
21. Smith, L.L. Causes of delayed onset muscle soreness and the impact on athletic performance: A review. *J. Strength Cond. Res.* **1992**, *6*, 135–141.
22. Raglin, J.S. Psychological factors in sport performance. *Sports Med.* **2001**, *31*, 875–890. [\[CrossRef\]](#)
23. Riebe, D.; Ehrman, J.K.; Liguori, G.; Magal, M. *ACSM’s Guidelines for Exercise Testing and Prescription*; Wolters Kluwer: Riverwood, IL, USA, 2018.
24. Ballmann, C.G.; Maze, S.B.; Wells, A.C.; Marshall, M.M.; Rogers, R.R. Effects of short-term Rhodiola Rosea (Golden Root Extract) supplementation on anaerobic exercise performance. *J. Sports Sci.* **2019**, *37*, 998–1003. [\[CrossRef\]](#)
25. Cui, Y.; Wang, Y.; Liu, G. Protective effect of Barbaloin in a rat model of myocardial ischemia reperfusion injury through the regulation of the CNPY2-PERK pathway. *Int. J. Mol. Med.* **2019**, *43*, 2015–2023. [\[CrossRef\]](#)

26. Ustunova, S.; Takir, S.; Yilmazer, N.; Bulut, H.; Altindirek, D.; Ng, O.H.; Tansel, C.D.; Dogan, B.S.U.; Ozbek, U.; Armutak, E.I. Hydrogen sulphide and nitric oxide cooperate in cardioprotection against ischemia/reperfusion injury in isolated rat heart. *In Vivo* **2020**, *34*, 2507–2516. [[CrossRef](#)] [[PubMed](#)]
27. Grove, J.R.; Prapavessis, H. Preliminary evidence for the reliability and validity of an abbreviated profile of mood states. *Int. J. Sport Psychol.* **1992**, *4*, 45.
28. Covington, A.C.; Rogers, R.R.; Kopec, T.J.; Ballmann, C.G. The Effect of Walking an Unfamiliar Versus Companion Dog on Mood, Exercise Enjoyment, and Heart Rate: A Pilot Field. *Top. Exerc. Sci. Kinesiol.* **2021**, *2*, 3.
29. Allen, J.D.; Mattacola, C.G.; Perrin, D.H. Effect of microcurrent stimulation on delayed-onset muscle soreness: A double-blind comparison. *J. Athl. Train.* **1999**, *34*, 334. [[PubMed](#)]
30. Connolly, D.A.; Sayers, S.P.; McHugh, M.P. Treatment and prevention of delayed onset muscle soreness. *J. Strength Cond. Res.* **2003**, *17*, 197–208.
31. Wei, J.; Carroll, R.J.; Harden, K.K.; Wu, G. Comparisons of treatment means when factors do not interact in two-factorial studies. *Amino Acids* **2012**, *42*, 2031–2035. [[CrossRef](#)] [[PubMed](#)]
32. Fritz, C.O.; Morris, P.E.; Richler, J.J. Effect size estimates: Current use, calculations, and interpretation. *J. Exp. Psychol. Gen.* **2012**, *141*, 2–18. [[CrossRef](#)]
33. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Erlbaum Associates: Hillsdale, MI, USA, 1988.
34. Megale, R.Z.; Deveza, L.A.; Blyth, F.M.; Naganathan, V.; Ferreira, P.H.; McLachlan, A.J.; Ferreira, M.L. Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: A systematic review of randomized, placebo-controlled trials. *J. Pain* **2018**, *19*, 475.e1–475.e24. [[CrossRef](#)]
35. Kindler, S.; Samietz, S.; Houshmand, M.; Grabe, H.J.; Bernhardt, O.; Biffar, R.; Kocher, T.; Meyer, G.; Völzke, H.; Metelmann, H.-R. Depressive and anxiety symptoms as risk factors for temporomandibular joint pain: A prospective cohort study in the general population. *J. Pain* **2012**, *13*, 1188–1197. [[CrossRef](#)] [[PubMed](#)]
36. Hernandez-Reif, M.; Field, T.; Krasnegor, J.; Theakston, H. Lower back pain is reduced and range of motion increased after massage therapy. *Int. J. Neurosci.* **2001**, *106*, 131–145. [[CrossRef](#)] [[PubMed](#)]
37. Kent, J.M.; Coplan, J.D.; Gorman, J.M. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. *Biol. Psychiatry* **1998**, *44*, 812–824. [[CrossRef](#)]
38. Izumi, T.; Kitaichi, Y.; An, Y.; Inoue, T.; Yoshioka, M. *The Amygdala Is the Target Brain Site of Anxiolytic Effects of SSRIs*; Nova Biomedical Books: Hauppauge, NY, USA, 2018.
39. Peñailillo, L.; Blazevidh, A.; Numazawa, H.; Nosaka, K. Rate of force development as a measure of muscle damage. *Scand. J. Med. Sci. Sports* **2015**, *25*, 417–427. [[CrossRef](#)] [[PubMed](#)]
40. Morgan, W.P.; Costill, D.L.; Flynn, M.G.; Raglin, J.S.; O'Connor, P.J. Mood disturbance following increased training in swimmers. *Med. Sci. Sports Exerc.* **1988**, *44*, 125. [[CrossRef](#)]
41. Hieronymus, F.; Lisinski, A.; Nilsson, S.; Eriksson, E. Influence of baseline severity on the effects of SSRIs in depression: An item-based, patient-level post-hoc analysis. *Lancet Psychiatry* **2019**, *6*, 745–752. [[CrossRef](#)]