The Effects of a Multi-Ingredient Dietary Supplement on Recovery from Delayed-Onset Muscle Soreness

Original Research

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Open Access

Published: June 10, 2024

Journal of Exercise and Nutrition: *2024, Volume 7 (Issue 1): 8*

ISSN: 2640-2572

Abstract

Introduction: The purpose of this investigation was to determine the effects of multi-ingredient dietary supplement on indices of muscle recovery on delayed-onset muscle soreness (DOMS).

Methods: In a randomized, placebo-controlled trial, healthy exercise-trained subjects (n=24) consumed the treatment (i.e., Caraflame®: Retinyl Palmitate (Vit. A) 3.3 mg, Sodium Butyrate 175 mg, and Beta-Caryophyllene 30 mg or placebo (i.e., Maltodextrin 1000mg) daily over 14 days. Subjects completed the DOMS protocol and were assessed for changes in pain (visual analog scale (VAS), strength (1-RM), and inflammatory markers (Interleukin-1β, Interleukin-6, and C-reactive protein). A dependent samples t-test was used to determine differences between groups regarding the delta score. A of $P \leq 0.05$ was used to assess significance.

Results: All subjects were physically active, healthy adults (Mean ± SD – Age 23.5 ± 7.0, Height 170.0 ± 12.7 cm, Body Mass 71.0 ± 19.57 kg, % body fat 24.3 ± 10.6). A significant difference was found for the assessment of pain threshold via VAS (p= 0.0126). Subjects in the treatment group exhibited a higher pain threshold two days post-DOMS (i.e., delta score data). Moreover, there were no significant differences between groups for 1-RM strength (p=0.1548). Furthermore, there were no significant changes in inflammatory markers (CRP p=0.9998, IL-6 p=0.9677, and IL-1β p=0.9184).

Conclusions: Based on this preliminary investigation, two weeks of a multi-ingredient dietary supplement may decrease the subjective perception of delayed-onset muscle soreness in exercise-trained adults.

Key Words: pain, exercise, nutrition

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Introduction

Delayed-onset muscle soreness (DOMS) is the pain typically occurring 1-2 days after engaging in unfamiliar physical activity, particularly eccentric loading[1]. The exact cause of DOMS is not entirely understood, but several theories suggest contributing factors. It may be due to microscopic tears in skeletal muscle, an inflammatory response to

exercise, or connective tissue damage[2-5]. It's important to note that DOMS is a natural part of the adaptation process, especially when muscles are subjected to new types of exercise. The soreness tends to decrease as the body adapts to the exercise.

Interleukin-6 (IL-6), Interleukin-1 beta (IL-1β), and C-reactive protein (CRP) are all involved in the immune response and inflammation. IL-6 is a pro-inflammatory cytokine produced by various cells, including immune cells, fibroblasts, and endothelial cells[6]. IL-1β is another pro-inflammatory cytokine that is part of the interleukin-1 family[7]. It is produced by immune cells in response to infection or injury. CRP is an acute-phase protein produced by the liver in response to inflammation. It is a marker of systemic inflammation and is often used clinically to assess the presence and severity of inflammatory conditions[6,8]. Elevated CRP levels in the blood indicate the presence of inflammation. Inflammation related to DOMS can lead to localized swelling and pain[9]. Additionally, exercise increases reactive oxygen species (ROS) production[10]. High levels of oxidative stress which can hinder muscle regeneration and contribute to muscle weakness[10,11].

Research has explored different methods and dietary supplements to alleviate symptoms associated with DOMS[12,13]. Anti-inflammatories are thought to help mitigate symptoms of delayed onset muscle soreness by modulating the inflammatory response. Antioxidant supplementation is believed to lower oxidative stress, allowing the body to heal. Vitamin A is a fat-soluble vitamin that is crucial for maintaining healthy vision and supports the normal functioning of the immune system. It is involved in regulating cell growth, differentiation, and proliferation. Vitamin A has antioxidant properties that help mitigate the production of free radicals[14]. Although there is scarce research on vitamin A's benefits in exercise-induced muscle damage, its antioxidant properties make it a potential supplement in enhancing recovery. Sodium butyrate is a type of salt derived from the short-chain fatty acid butyric acid. It is naturally occurring in some foods and used as a dietary supplement geared towards improving gastrointestinal health[15,16]. Studies have demonstrated that sodium butyrate suppresses NF-κB activation[16]. This reduces the production of inflammatory cytokines and reduces markers of inflammation, such as CRP[17]. Beta-Caryophyllene is a natural compound occurring in plants. It exerts its effects on the endocannabinoid system, which plays a role in physiological functions, including muscle contractility, immune function, and inflammation[18]. This ingredient acts as an anti-inflammatory and has analgesic properties. Evidence suggests Beta-Caryophyllene combats chronic inflammation by inhibiting the production of inflammatory mediators, IL-1β, and IL-6[18]. Endocannabinoid receptors, CB1 and CB2, are found in peripheral tissues such as the muscles and joints[18]. BCP can bind to these receptors, affecting pain perception at the site of injury or inflammation[18].

The adverse impacts of DOMS, particularly muscle soreness and stiffness, can hinder training and athletic performance. Supplementation might help alleviate DOMS and improve recovery. The purpose of this investigation was to determine the effects of a multi-ingredient dietary supplement on indices of muscle recovery after a delayed-onset muscle soreness (DOMS) protocol. The authors hypothesize the dietary supplement will lessen the inflammatory response, leading to improved decreased pain and maintenance of strength.

Methods

Experimental Protocol

In a randomized, placebo-controlled trial, healthy exercise-trained subjects consumed the treatment (i.e., Caraflame®: Retinyl Palmitate (Vit. A) 3.3 mg, Sodium Butyrate 175 mg and Beta-Caryophyllene 30 mg) or placebo (i.e., maltodextrin 1000 mg) daily over 14 days. Subjects visited the lab on four separate occasions. During the first visit, subjects completed body composition assessment and exercise/supplement history and were provided with the supplement with instructions. Subjects returned to the laboratory on day 7 to complete baseline soreness assessment, DOMS protocol, strength assessment, and provide a salivary sample. During visits 3 (day 8) and 4 (day 9), subjects completed a soreness and strength assessment and were provided salivary samples. Subjects were instructed to not change any of their dietary habits and abstain from resistance training during the study. All participants underwent an informed consent process in accordance with the Declaration of Helsinki and an approved IRB protocol submitted to the institutional review board of Keiser University.

Body Composition Assessment

Body composition was assessed using a multi-frequency bioelectrical impedance device (InBody® 270). Study participants stood on the platform of the device barefoot with the soles of their feet on the electrodes and then grasped the handles of the unit with their thumb and fingers to maintain direct contact with the electrodes. They stood still for

~1 minute while keeping their elbows fully extended and their shoulder joint abducted to about a 30-degree angle. This method has been described previously[19].

Delayed Onset Muscle Soreness Protocol

Subjects performed DOMS protocol with the non-dominant arm. Subjects were instructed to place their elbow on the pad of the exercise bench with their shoulders flexed at 45 degrees. Subjects held a dumbbell weighing 60% of their 1RM for one second at a 90-degree angle before lowering it slowly for three seconds. Once the elbow was completely extended, the investigator manually returned the subject's arm to a 90-degree flexion position. Subjects completed 75 repetitions with their non-dominant arm using this method. Protocol was ended if subjects were unable to complete repetitions with proper form.

Assessment of self-reported ratings of soreness

To assess subjective ratings of soreness and to determine the level of soreness, subjects were instructed to complete, subjects rated their soreness using a number scale. The numeric rating ranged from 0 to 10. Zero (0) indicated none or no soreness, five indicated moderate soreness, and 10 indicated severe soreness. Subjects completed this assessment on each visit to the laboratory.

One-repetition maximum of the elbow flexors

Strength was assessed via a 1-RM (one repetition maximum) of the elbow flexors of both arms. Each subject was allowed to perform 2-3 warm-up sets. Subsequently, the investigator selected an appropriate weight to determine their maximal strength. Each subject was given three total attempts at their 1-RM.

Inflammatory Markers (IL-6, IL-1β and CRP)

Saliva samples were obtained from each participant via passive drool. The samples were collected in 1.5 mL polypropylene microcentrifuge tubes and kept on ice until the session was complete. Following the session, the samples were stored in a freezer at -20°C until assayed. Saliva samples were run in duplicates. All inflammatory markers (IL-6, *IL-1β,* and CRP) were quantified via a human enzyme immunoassay kit according to the manufacturer's instructions (Salimetrics, Carlsbad, CA, USA). The functional sensitivity of the Salivary CRP ELISA Assay kit (Generation II) is 19.44 pg/mL when the sample is diluted two-fold. The functional sensitivity of the salivary IL-6 ELISA is 2.08 pg/mL. The functional sensitivity of the salivary IL-1β ELISA is 0.6 pg/mL.

Statistical Analysis

All data are expressed as the mean ± standard deviation. A dependent samples t-test was used to determine differences between groups with regard to the delta score. A p-value of $P<0.05$ was used to assess significance.

Results

Subjects

Table 1 shows subject characteristics. All subjects (n=24) were young, healthy adults who trained regularly.

Table 1: Subject characteristics.

	Treatment (4 male, 8 female)	**Placebo (5 male, 7 female)**
Age years	26 ± 9	21 ± 1
Height cm	168.2 ± 14.5	171.7 ± 11.0
Body mass kg	70.8 ± 23.7	71.2 ± 15.3
Lean body mass kg	51.1 ± 22.3	56.4 ± 15.2
Fat mass kg	19.7 ± 7.9	14.9 ± 6.5
% Fat	27.5 ± 11.5	21.2 ± 9.1
Total body water liters	39.3 ± 13.7	41.2 ± 11.1
Total years of training	9 ± 10	8 ± 5
Mean hours of cardio/week	5 ± 2	5 ± 2
Mean hours of weight-training/week	2 ± 1	4 ± 7
Other exercise/week	1 ± 1	2 ± 4

Data are expressed as the mean ± standard deviation.

Indices of Recovery

There were significant differences between groups at 48 hours post for the delta score of perceived muscle soreness (Table 2). The treatment group had lower perceived muscle soreness. No differences were found for the strength assessment (1-RM of the non-dominant elbow flexors) (Table 3). There were no changes in CRP, IL-1beta, or IL-6 in the treatment or placebo groups (Figure 1).

Table 2 : VAS for assessing muscle soreness.

	Baseline	**24 h post-DOMS**	**Delta**	**P value of the delta**
Treatment	1.2 ± 2.3	3.8 ± 2.2	2.7 ± 2.5	0.8798
Placebo	0.9 ± 1.4	4.0 ± 2.5	3.1 ± 2.3	
	Baseline	**48 h post-DOMS**	**Delta**	**P value of the delta**
Treatment	1.2 ± 2.3	3.4 ± 1.9	2.3 ± 2.5	*0.0126**
Placebo	0.9 ± 1.4	5.8 ± 2.2	4.9 ± 2.2	

Data are expressed as the mean ± standard deviation * Statistically different between groups at 48 hours post-DOMS protocol P<0.05. The effect size (Cohen's d) for the delta at 48 h post is 1.104 (large effect size). The 95% confidence interval for the treatment is 0.6443-3.856, and the placebo is 3.497-6.336.

Table 3: Strength Assessment (1 RM).

	Baseline	**24 h post-DOMS**	**Delta**	**P value of the delta**
Treatment	11.4 ± 6.1	10.4 ± 6.2	-1.0 ± 1.8	0.2339
Placebo	12.5 ± 6.7	9.8 ± 6.9	-1.6 ± 1.6	
	Baseline	**48 h post-DOMS**	**Delta**	**P value of the delta**
Treatment	11.4 ± 6.1	10.8 ± 6.4	-0.6 ± 1.7	0.1548
Placebo	12.5 ± 6.7	10.9 ± 6.9	-1.6 ± 1.6	

Data are expressed as the mean ± standard deviation. There were no between-group differences.

Figure 1. Inflammatory markers.

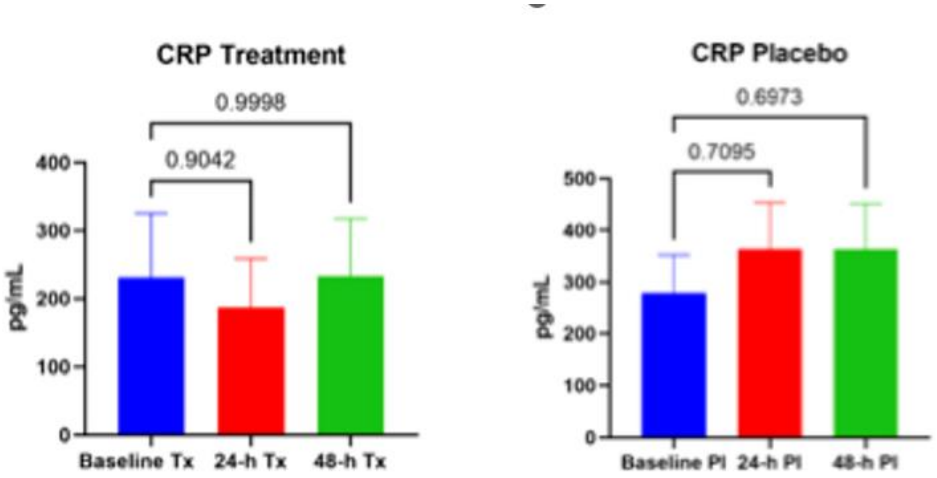
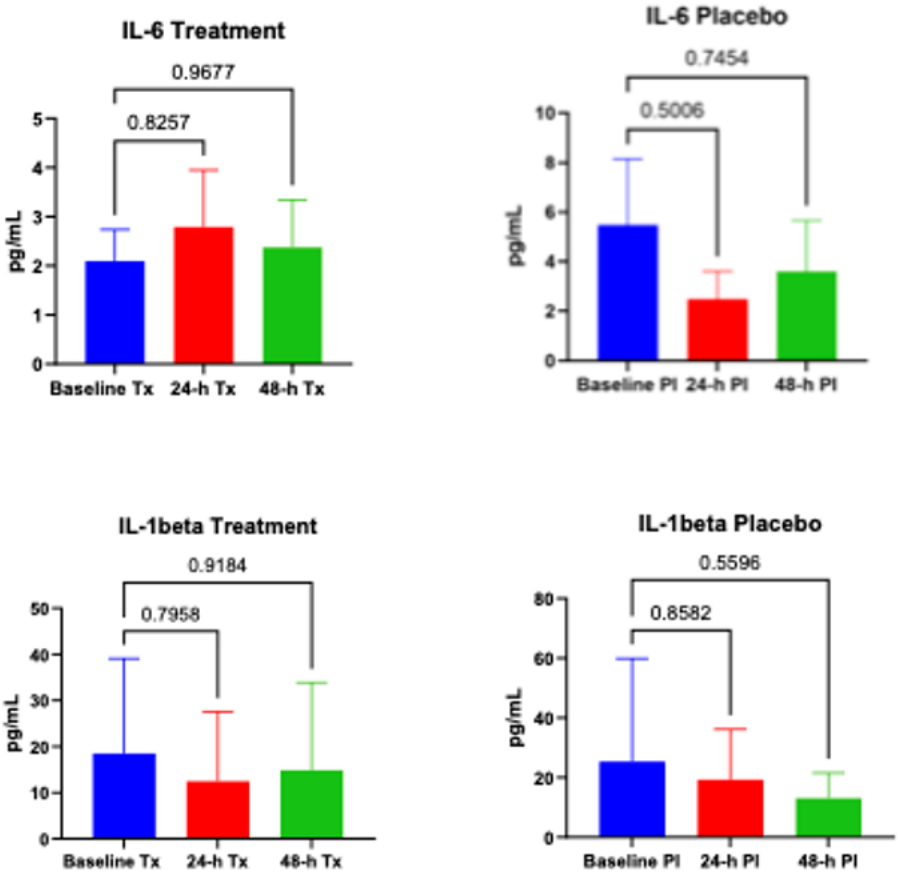


Figure 2. Continued.



Data are expressed as the mean ± standard deviation.

Discussion

This study investigated the effects of 14 days of supplementation with a multi-ingredient supplement on indices of recovery following exercise-induced muscle damage. The major findings of the current investigation are that this supplement reduced the perception of pain via VAS. No improvements were found between the groups in 1-RM or inflammatory markers.

During intense or unfamiliar physical activity, microscopic damage occurs to the muscle fibers and connective tissue[20]. Following muscle damage, various inflammatory mediators are released locally. These include cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β)[21]. These cytokines signal the body to begin the repair process. Increases in inflammatory markers such as IL-6 are correlated with the intensity and duration of exercise[9,22]. As the healing process continues, anti-inflammatory markers are released, and inflammation begins to subside[6]. An excessive or prolonged inflammatory response can dampen the body's ability to repair and recover[9,22]. This study did not report any changes in the inflammatory markers CRP, interleukin-6 (IL-6), and interleukin-1β (IL-1β). It is possible that the exercise protocol was not sufficient to elicit an inflammatory response. Additionally, the small sample size may explain the lack of expected change in inflammatory markers. Subjects did report decreases in muscle soreness. It is not clear why there can be an inflammatory response or microscopic muscle injury, and yet there is no pain. On the other hand, subjects may feel subjective pain without any changes in inflammation. This may explain the decrease in subjective pain in the absence of changes in inflammatory markers.

Vitamin A exhibits anti-inflammatory properties. Vitamin A neutralizes free radicals which cause cellular damage and inflammation [14]. These antioxidant properties contribute to its role in decreasing inflammation. In an animal study, the experimental group was subjected to an exercise regimen with vitamin A supplementation. Inflammatory markers (L-1β, TNF-α, IL-10, and HSP70) and antioxidant enzyme activity were assessed after eight weeks[14]. Pro-inflammatory

markers (IL-1β and TNF-α) were higher in the exercise and exercise + vitamin A group compared to the sedentary group. A significant decrease in IL-10 was reported in the exercise + vitamin A group. This study suggests vitamin A decreases stress markers and impairs antioxidant capacity. Similarly, Gasparotto et al. [22] reported an increase in oxidative stress and a decrease in IL-10 in rats following aerobic exercise and supplementation with vitamin A. The authors theorize vitamin A interferes with the anti-inflammatory response by decreasing levels of IL-10[14,23]. Although the studies demonstrate Vitamin A's potential to mitigate oxidative stress, comparisons between animal and human studies should be made with caution. This study did not observe any differences between groups in inflammatory markers.

Numerous studies report the anti-inflammatory effects of sodium butyrate; however, none of these studies involve inflammation related to exercise-induced muscle damage[16,17,24]. Butyrate has shown to alter the inflammatory response in gastrointestinal cells, leading researchers to explore its potential effects on systematic inflammation [25]. An in vitro study conducted by Säemann et al. [26] reported sodium butyrate decreased the production of the pro-inflammatory TNF-α and increased levels of the anti-inflammatory cytokine IL-10 in a dose-dependent manner. Other studies report inhibition of NF-kB leading to a reduction in pro-inflammatory cytokines[25,27]. It is plausible that the DOMS protocol utilized in this study did not elicit a sufficient inflammatory response or that sodium butyrate is not effective for acute changes in inflammation related to exercise. Meijer et al.[25] theorize butyrate's anti-inflammatory effects are dependent on cell type. Additionally, the small sample size may account for the lack of hypothesizes change in inflammatory markers.

Research suggests β-Caryophyllene exhibits both anti-inflammatory and analgesic effects[18,28,29]. β-Caryophyllene is a dietary cannabinoid that selectively binds to the CB2 receptors in the endocannabinoid system. This results in a reduction of pain[28]. Amalraj et al. [29]evaluated the effects of liposomal β-caryophyllene formulation on blood markers (creatine kinase (CK) and myoglobin), pain, and isometric strength related to DOMS. The DOMS-inducing protocol consisted of six sets of 10 maximal eccentric isokinetic muscle actions of the forearm flexors at a velocity of 30° s^{-1} . Outcomes were assessed immediately after exercise protocol, 24 h, 48 h, and 72 h. No changes in blood parameters and a slight increase in isometric strength were found. Similar to our study, subjects reported significantly reduced pain via VAS. BCP reduces the production of pro-inflammatory mediators[18,29]. Reducing inflammation in the muscle can reduce pain. BCP can decrease acute pain via the endocannabinoid system and indirectly activates μ-opioid receptors[18,29]. This contributes to a decrease in short-term pain perception. The anti-inflammatory and analgesic properties found in BCP may account for the reduction in perceived muscle soreness in this study.

A major limitation of this study is the small sample size. large sample sizes are much better for these types of randomized control trials, however funding for this study was limited. It is essential to interpret these findings with caution as they may not be representative of the larger population.

Conclusions

The results of this study suggest that this multi-ingredient supplement may potentially inhibit the perception of pain two days after inducing muscle soreness. The mechanism(s) for this is unclear but may be related to the key ingredient, beta-caryophyllene, which may decrease pain.

Acknowledgments

This study was funded in part by a grant from Nutrition Formulators (Miramar, FL) to the ISSN.

Disclosures

Jose Antonio is the CEO of the academic non-profit ISSN (a 501c3). The ISSN receives donations from companies that market, sell, or manufacture dietary supplements. No other authors have any COI to declare.

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