THE EFFECTS OF CANNABIDIOL ON MEASURES OF PERFORMANCE FOLLOWING ECCENTRIC EXERCISE

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ABSTRACT

BRETT CROSSLAND

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Following intense exercise, there is a period of time when performance is decreased. Cannabidiol (CBD) is advertised as an anti-inflammatory supplement that can expedite recovery when consumed after exercise. The purpose of this study was to determine if CBD supplementation reduces fatigue and inflammation, and enhances performance, following eccentric exercise. A double-blind, placebo controlled, repeated measures crossover design was used. Twenty-four well-trained female participants (age = 21.2 ± 1.8 yrs., height = 166.4 ± 8 cm, weight = 64.9 ± 9.1 kg) were randomized to receive 5 mg/kg of CBD in pill form or a placebo 2 hrs prior to, immediately following, and 10 hrs following muscle damage. For each treatment, 100 repetitions of unilateral eccentric leg extension were completed to induce muscle damage. Blood was collected, and performance and fatigue were measured prior to, and 4 hrs, 24 hrs, and 48 hrs following the muscle damage. Blood samples were analyzed for concentrations of myoglobin (Mb) and inflammatory markers (IL-10, IL-1β, and IL-6). Fatigue was measured utilizing a visual analogue fatigue scale. Performance was measured across five variables: vertical jump (cm), peak dynamic knee extensor torque at 60, 180, and 300°/sec (N· m), and peak isometric knee extensor torque (N· m). Approximately 28 days separated treatment administration to control for the menstrual cycle. No significant differences (p = 0.573) were observed between the treatments for any inflammatory marker. Peak torque at 60°/sec (p = 0.001) and peak isometric torque (p = 0.02) were significantly lower 24 hrs following muscle damage, but none of the five measured performance variables were significantly different (p >

0.05 for all) between treatments at any time point. A significant increase ($p = 0.002$) in Mb concentrations was observed across treatments 4 hrs following muscle damage, but no significant differences ($p = 0.12$) were observed between treatments at any timepoint. Subjective fatigue was not significantly different ($p = 0.13$) between the treatments at any timepoint. CBD supplementation was unable to reduce fatigue, limit inflammation, or restore performance in well-trained female athletes.

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CHAPTER I

INTRODUCTION

The health benefits of exercise are well established through research (e.g., Warburton et al., 2006). While exercise has numerous documented benefits, there is a period of time following exercise when individuals are unable to adequately perform due to fatigue (Ament & Verkerke, 2009). Immediately following strenuous exercise, there is an observable drop in performance that can last from hours to several days depending on the intensity, duration, and type of exercise (Armstrong et al., 1991). The underlying factors affecting this decrease in performance include myofibrillar disruption (Hortobágyi et al., 1998), swelling (Cleak & Eston, 1992), reduced range-of-motion (Ebbeling & Clarkson, 1990), an efflux of enzymes and proteins (Dekkers et al., 1996), and the inflammatory process (Hyldahl, & Hubal, 2014). These intercellular interactions can influence the time it takes to restore previous performance levels (Peake, Neubauer, Della Gatta, & Nosaka 2017). An inability to fully recover from strenuous bouts of exercise can increase the risk of injury and severely limit optimal performance (Soligard et al., 2016).

While the exact time to fully regain performance capabilities cannot be precisely known for each athlete, a single muscle damaging session typically results in a loss of strength and aerobic capabilities for up to 4 days (Byrne & Eston, 2002; Sargeant & Dolan, 1987). For many, methods of optimal recovery from strenuous exercise and a rapid return to performance remain elusive. The primary goal of recovery from exercise for athletes and those who regularly engage in recreational exercise is aimed at a reduction in muscle soreness, and therefore a decreased time to the return of performance. Several methods to expedite the recovery from strenuous exercise have been documented. The methods that have shown some benefit are massage

(Hemmings et al., 2000), stretching (Torres et al., 2013), water immersion (Leeder et al., 2012), nutrition (Kreider et al., 2010), and supplements (Calleja-González et al., 2016).

The market for sports nutrition was estimated to be nearly $12 billion in 2016 with an expected average growth rate of 5% (Aoyagi & Ikeda, 2019). A significant amount of research has been conducted in this area, with over 2,000 articles published in 2017 alone (Kerksick et al., 2018). Specifically, much of the focus has included nutritional products that are advertised to aid in the recovery from exercise. For example, branched chain amino acid supplementation may decrease muscle soreness following strenuous exercise (Hormoznejad et al., 2019). A milk-based carbohydrate and protein supplement may increase isokinetic muscle performance and decrease muscle damage, when compared to a placebo, following eccentric exercise-induced muscle damage (Cockburn et al., 2008). Whey protein supplementation may significantly reduce isometric knee extension strength loss following an eccentric muscle damaging protocol (Cooke et al., 2010).

Recently, cannabidiol (CBD), which has been purported to aid in the recovery from strenuous exercise by decreasing inflammation and muscle damage (Miller, 2019), has gained popularity. While there have been some significant benefits found with CBD supplementation (e.g., improved symptoms in select neurological disorders; Cheng et al., 2014; Devinsky et al., 2016; Devinsky, Patel, Cross et al., 2018), to date, no research has been conducted to validate the claim that CBD can attenuate exercise-induced muscle damage and inflammation.

The passing of the 2018 Farm Bill legalized the production and sale of hemp-derived cannabis products, which had previously been illegal under the Controlled Substances Act passed in 1970 (Mead, 2019). Hemp, which is aesthetically similar to marijuana, has a unique chemical content. Hemp contains less than 0.3% tetrahydrocannabinol (THC), the psychoactive

component of the plant, while marijuana typically contains 10 to 15% THC (Holler et al., 2008). The legalization of hemp allowed for the development and distribution of a large number of hemp-derived products. A significant increase in the production and distribution of CBD has been observed following the passing of the 2018 Farm Bill Act (Smith et al., 2018). According to market research, CBD sales were over $600 million in 2018, and are expected to be more than $20 billion by 2022 (Benson, 2019)

CBD is one of over 100 cannabinoids found in the cannabis plant (Corroon & Knight, 2018). In hemp, CBD is the most abundant cannabinoid (Sawler et al., 2015). In marijuana, THC is the most abundant cannabinoid (Sawler et al., 2015). There are two primary forms of CBD supplements: isolate and full spectrum. Full spectrum CBD supplements contain all of the cannabinoids and terpenes naturally found in hemp (Maroon et al., 2015). CBD isolate supplements contain only CBD and trace amounts of other cannabinoids and terpenes (Maroon et al., 2015). Supplements containing CBD may be consumed via pills, lotions, tinctures, gum, powder, or edibles, with each delivery method resulting in variable bioavailability (Millar et al., 2018). This includes concentrations and time to peak concentration (Millar et al., 2018).

The therapeutic benefit of CBD supplementation may be useful with a variety of conditions. Specifically, CBD supplementation may improve aspects of health with neurological disorders. Devinsky et al. (2016) found a 36% reduction in motor seizures over a 12-week period in adults with epilepsy who consumed CBD (Devinsky et al., 2016). CBD may significantly reduce seizure frequency by 43% over a 14-week period in children with Dravets syndrome (Devinsky, Patel, Theile et al., 2018). In patients with Lennox-Gastaut syndrome, a 20 mg/kg daily dose of CBD may reduce seizures by 42% (Devinsky, Patel, Cross et al., 2018). Supplementation with CBD may assist in combatting the progression of Alzheimer's disease,

and improving biopsychosocial characteristics such as social withdraw and facial recognition (Cheng et al., 2014). The positive effects of CBD are likely due to an ability to reduce neural inflammation, likely through reducing microglial cell migration and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling (Fernández-Ruiz et al., 2013).

The cardioprotective benefits of CBD supplementation have also been observed in animal studies. A single dose (10 or 20 mg/kg) elicited a significant reduction in heart rate and blood pressure responses to stress in Wistar rats (Resstel et al., 2006). Durst et al. (2007) found that 5 mg/kg of CBD was able to significantly reduce infarct size, leukocyte count, and interleukin-6 (IL-6) concentrations after 7 days of treatment in mice. In diabetic mice, CBD may significantly reduce cardiac dysfunction through a reduction in myocardial inflammation and oxidative stress (Rajesh et al., 2010). While a large portion of the significant findings with regards to the cardioprotective effects of CBD are in animal models, there is evidence that these results may prove beneficial in humans. More specifically, a single 600 mg dose of CBD led to a significant reduction in resting systolic blood pressure for human participants (Jadoon et al., 2017).

While the anti-inflammatory effects of CBD supplementation have been investigated across a number of different chronic conditions, these effects have not been characterized within healthy human skeletal muscle. Recent unpublished data from the research team's lab investigating the effects of CBD on human skeletal muscle cells grown in culture resulted in a significant increase in the gene expression of myogenin, a major regulator of muscle growth and repair (myogenesis), in response to CBD treatment *in vitro*. CBD may therefore have a beneficial effect on the muscle following exercise, and warrants further investigation. Additionally, on a limited sample size of two culture samples per group, the research team found potential effects, however not statistically significant, of CBD treatment in the context of an

lipopolysaccharide (LPS)-induced inflammatory response. From this pilot data, the team observed that the expression of genes related to myogenesis were decreased by 84% (Myogenin) and 75% (MyoD) in LPS-treated myotubes, while only decreased by 63% and 18%, respectively in LPS treated myotubes that were also exposed to CBD. As expected, the gene expression for superoxide dismutase 2 (SOD2), which helps manage reactive oxygen species (ROS) in the cell, was increased approximately 5-fold in the LPS condition, as part of the natural inflammation response. Interestingly, in the LPS+CBD condition, SOD2 was increased more than 17-fold. Therefore, CBD may greatly enhance antioxidant support within inflamed skeletal muscle.

In order to fully understand the benefit of CBD supplementation, a more comprehensive body of research that includes muscle-damaging protocols in human participants must be completed. It is the hope of the current researchers to begin to investigate the effects of CBD supplementation on markers of muscle damage and inflammation following an acute bout of eccentric exercise.

Statement of the Problem

CBD was the top-selling dietary supplement in 2018, accounting for over $52.7 million in U.S. sales (Smith et al., 2019). The supplement is advertised as an aid in the recovery from exercise. However, there is currently very limited research investigating CBD's effectiveness following intense exercise. In order for consumers to be aware of this potential benefit from CBD, it is imperative that research with this supplement be conducted. Therefore, the purpose of this study is to investigate if CBD supplementation is able to attenuate loss of performance, muscle damage, and inflammation following acute, strenuous, eccentric exercise in female collegiate athletes.

Hypotheses

This research study investigates the effects of cannabidiol supplementation on markers of muscle damage, inflammation, and performance. The hypotheses tested in this study are as follows:

1. Cannabidiol supplementation will have a significantly greater protective effect against muscle damage than the placebo, as measured by plasma levels of myoglobin, in collegiate female athletes.
2. Cannabidiol supplementation will attenuate the inflammatory cytokine (e.g., interleukin-6, interleukin-1β) response following eccentric exercise when compared to the placebo in collegiate female athletes.
3. Cannabidiol supplementation will allow for an increase in measures of isokinetic and isometric strength after 24 and 48 hrs compared to the consumption of a placebo in collegiate female athletes following eccentric exercise-induced muscle damage.

Definitions

Supplement: Product taken orally that contains a dietary ingredient intended to supplement the diet.

Cannabidiol (CBD): One of over 120 cannabinoids found on the cannabis plant, and makes up roughly 40% of the hemp plant. CBD ingestion results in no psychoactive effects, and is well tolerated in humans at high dosages (>1000 mg/day).

Cannabis: A tall herb with tough fiber consisting of three plants that vary by chemical composition: Cannabis sativa, Cannabis indica, and Cannabis ruderalis.

Marijuana: A popular drug derived from the cannabis plant. Marijuana contains roughly 10 to 15% THC, which is the cannabinoid responsible for the psychoactive properties of marijuana.

Hemp: Part of the Cannabis sativa family and is grown for its industrial and medical uses. Hemp contains less than 0.3% THC, with CBD being the highest occurring cannabinoid in the hemp plant.

Exercise-induced muscle damage (EIMD): Characterized by symptoms that occur both immediately and for up to 14 days following an exercise bout. The main result of EIMD is loss of skeletal muscle function and soreness (Owens et al., 2019).

Exercise-induced inflammation: A systemic cytokine release following exercise consisting of pro-inflammatory and anti-inflammatory responses (Suzuki, 2018).

Assumptions

The assumptions of this study are:

1. The participants will complete each exercise session as directed by the researcher.
2. The participants will make no significant changes to their normal exercise, sleeping, or eating habits throughout the entirety of the study.
3. The participants will continue to consume their regular dietary practices throughout the study.
4. The participants will arrive for all testing sessions fasted for 10 hrs prior to arrival.
5. The participants will accurately and honestly report the timing of their menstrual cycle.

Delimitations

The delimitations of this study are:

1. Results of the study will be based upon the researchers' choice of dosage and timing of the supplement, which may be suboptimal in eliciting a therapeutic benefit.
2. The results will be reported with female collegiate athletes.

Significance of Study

While there is evidence of a potential benefit, to date, limited research has been performed investigating the effects of CBD on exercise performance or recovery from strenuous exercise in any human population. This study will mark the first investigation into effects of CBD supplementation on serum markers of inflammation following strenuous exercise. With the results of this study, researchers will gain a better understanding of how CBD may influence muscle damage, performance, and inflammation. In addition, the results of this study will serve to inform consumers of CBD, coaches, trainers, and other healthcare professionals to their potential benefit in restoring markers of performance following strenuous exercise.

CHAPTER II

REVIEW OF THE LITERATURE

Cannabis

The Cannabis plant is a versatile fiber crop that has served many purposes throughout the years, including use in rope, clothing, food, building material, and medicine. The first medical use of the plant as an analgesic can be traced back to 200 A.D., but its industrial use has been documented back to 1500-1200 B.C. (Mikuriya, 1969). There are three primary varieties of Cannabis: Cannabis indica, sativa, and ruderalis. These three varieties differ only in their growth pattern and chemical makeup depending on the region in which they are grown. The chemical makeup of the Cannabis plant consists of cannabinoids, terpenes, and flavonoids. There are over 100 identified cannabinoids in Cannabis, with the two most abundant being THC and CBD. THC is the most abundant cannabinoid present in Cannabis and is the chemical responsible for the psychoactive effect of the plant. CBD, the second most abundant cannabinoid found in the Cannabis plant, has no psychoactive effect and may be beneficial with treating a number of medical conditions. Marijuana and hemp are the two primary forms of Cannabis and can be differentiated by their appearance, as well as the ratio of THC to CBD. Marijuana typically contains larger amounts of THC (5-30%) compared to CBD (<10%), while hemp contains larger amounts of CBD (20%) than THC (<0.3%; Hilderbrand, 2018). The chemical structure of CBD derived from marijuana and hemp are identical. However, most CBD supplements are typically derived from hemp due to the ease of the extraction process. The therapeutic benefits of THC and CBD have been researched with some significant findings reported. For the purposes of this research, only CBD is discussed.

The cannabinoid CBD was first isolated from the Cannabis plant by Roger Adams and colleagues in 1940, and researchers began investigating its potential effects shortly thereafter (Pertwee, 2006). The first documented research on CBD was performed in 1946 when Dr. Walter S. Loewe investigated the effects of CBD in mice and found that it did not hinder mental alertness (Loewe, 1946). Since 1946, ongoing research has been conducted investigating the effects of CBD on a number of medical conditions, including rheumatoid arthritis, epilepsy, diabetes, heart disease, multiple sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease (Consroe et al., 1991, Silvestro et al., 2019, Trapp & Nave, 2008). The research findings associated with CBD in regard to treating a large range of various conditions have been mixed. However, it appears that CBD is most effective in treating conditions associated with inflammation and oxidative stress (Zurier & Burstein, 2016).

Endocannabinoid System

Until 1992, the exact mechanism by which Cannabis elicited its psychoactive effects on humans was unclear. Munro et al. (1993) were the first researchers to isolate and clone the first of two cannabinoid receptors that make up the endocannabinoid system. The endocannabinoid system (ECS) is a neuromodulatory system that affects the central nervous system, regulating synaptic plasticity, and responding to endogenous and environmental stressors (De Petrocellis & Di Marzo, 2009). This system is vital for the maintenance of energy balance and body mass, drug addiction, immune function, and pain regulation (Eckardt et al., 2009). The ECS is comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes that interact with endocannabinoids (Mackie, 2008).

To date, two cannabinoid receptors have been identified: cannabinoid 1 receptor (CB1) and cannabinoid 2 receptor (CB2). Both receptor types are coupled through G proteins, and bind

negatively to adenylate cyclase, and positively to mitogen-activated protein kinase. Activation of CB1 and CB2 receptors can elicit a wide range of consequences on cellular physiology, including synaptic function (Howlett et al., 2002). CB1 receptors are primarily found in the central nervous system where their function is to inhibit neurotransmitter release. These receptors interact with THC and are responsible for the psychoactive effects of the marijuana plant. CB2 receptors are regulators of cytokine release throughout the body, but primarily in peripheral and immune cells. While CBD does not appear to act directly on either CB1 or CB2 receptors, it may indirectly act through a number of other receptors, such as the transient potential vanilloid receptor type-1, the 5-HT_{1A} serotonin receptor, and the orphan receptor GPR55 (Luvone et al., 2009).

Endocannabinoids are lipids that interact with the cannabinoid receptors and regulate various processes within the body. The two primary Endocannabinoids that have been identified are Arachidonylethanolamide, also known as anandamide, and 2-arachidonylglycerol (2-AG). While very similar in chemical structure, 2-AG and anandamide interact with different enzymatic pathways and elicit different physiological responses (Lu & Mackie, 2016). Both anandamide and 2-AG have a high affinity for CB1 receptors, while anandamide has little to no affinity for CB2 receptors and 2-AG is a CB2 receptor agonist (Sugiura et al., 2006). The baseline physiological levels of 2-AG and anandamide are regulated by two intracellular enzymes, fatty acid amide hydrolase (FAAH) and monoacyglycerol lipase (MAG-L; Di Marzo & De Petrocellis, 2012). While the exact mechanism by which CBD elicits its anti-oxidative and anti-inflammatory response remains unclear, it appears that CBD supplementation increases anandamide levels through the blunting of the expression and activity of FAAH, thereby signaling the ECS and decreasing NF-κB signaling (Luvone et al., 2009).

Safety and Dosage of Cannabidiol

It is evident that CBD is well tolerated by both humans and animals with minimal side effects across varying dosages. The most commonly reported side effects are tiredness, diarrhea, and changes in appetite (Iffland & Grotenhermen, 2017). No changes in psychomotor function, psychological function, or cardiovascular measures (e.g., blood pressure, heart rate) have been reported with high chronic doses (Bergamaschi et al., 2011). Perhaps the largest unknown that remains with the supplemental and medical use of CBD is a clear understanding of the proper dosage. Researchers have investigated dosages ranging from 1 mg/day up to 25 mg/day, and have found potential benefit, particularly in those with epilepsy and psychotic disorders, across these dosages (Iffland & Grotenhermen, 2017). The absorption rate and bioavailability of CBD is related to the method of administration. Intravenous administration elicits the highest blood plasma concentration with the time to peak concentration approximately equal to 3 mins (Ohlsson et al., 1986). The oral administration of CBD can be delivered by inhalation, oromucosal spray, sublingually, or with a capsule. Each method elicits a different maximum plasma concentration and time to reach maximum plasma concentration (Millar et al., 2018). Among the oral administration methods, inhalation elicits the highest bioavailability (31%), and oral capsule administration results in the lowest bioavailability (Cherniakov, 2017). There are no known clinically significant drug interactions with CBD at this time (Stout & Cimino, 2014).

Anti-Inflammatory Effects of Cannabidiol with Disease

The therapeutic effects of the Cannabis plant have been investigated on a variety of physical conditions. Much of the research has focused on animal models, but there is a growing number of research articles with human participants. Research on CBD has largely included studies in which the anti-inflammatory and antioxidative effects on various disease conditions

have been investigated (Iffland & Grotenhermen, 2017). To date, no research has been published examining the direct effects of CBD on EIMD and inflammation. Therefore, the potential anti-inflammatory and anti-oxidative capabilities of CBD in the context of specific inflammatory disease states are discussed.

Low-level inflammation is a critical factor in the development of osteoarthritis, a condition that is commonly treated with nonsteroidal anti-inflammatory drugs. Philpott et al. (2017) investigated the effects of CBD on lab-induced osteoarthritis in rats. Researchers induced osteoarthritis by anaesthetizing the animals and shaving down a section of the knee, and injected CBD into the joint. Following this, the researchers monitored variables associated with inflammation, including blood flow, rolling leukocytes, adherent leukocytes, and leukocyte traffic, over a 14-day period. During this time, the markers were measured in rats with and without CBD treatment administration ranging from 50 to 300 μg / 50 μL. The local application of CBD significantly reduced the acute markers of inflammation (i.e., rolling and adherent leukocyte count). Another main finding of this study was that 300 μg of CBD improved weight-bearing ability and led to a higher paw withdrawal threshold, indicating a reduction in the pain sensation associated with osteoarthritis (Philpott et al., 2017).

Malfait et al. (2000) had similar findings when investigating the effect of CBD on collagen-induced arthritis. Similar to Philpott et al. (2017), rodents were induced with an arthritic condition. Following the appearance of an arthritic condition, CBD was administered both orally and through injection at varying (50, 25, 10, 5, & 2.5 mg/kg) dosages daily for 10 days. Researchers measured tumor necrosis factor alpha (TNF-α) and ROS intermediate production levels, as well as arthritic changes, in the hind paw that was subjected to hyperplasia and destruction. Significant decreases in all measured variables were observed in the mice

treated with CBD at and above 5 mg/kg (when injected), and above 10 mg/kg (when administered orally). Researchers found dose-dependent responses that resembled a bell curve, when plotted for the measured variables via both oral and intraperitoneal injection. For the mice that received intraperitoneal injection, very little difference between the control and the 2.5 and 25 mg/kg doses was observed. The researchers found that 5 mg/kg elicited the optimal anti-inflammatory effect. For oral administration, researchers found that 25 mg/kg was the optimal dose. At these optimal dosages, there were no differences in the therapeutic effects, suggesting that oral administration of CBD can be an effective means of treatment (Malfait et al., 2000).

Intestinal inflammation is associated with conditions such as celiac disease, inflammatory bowel disease, and gastroenteritis (Sartor, 1994). The use of CBD, as a means of reducing intestinal inflammation, is a promising treatment. De Filippis et al. (2011) investigated the potential use of CBD in reducing inflammation associated with ulcerative colitis in human (male) participants and mice. The researchers found that a treatment of 10 mg/kg of CBD was able to reduce the upregulation of the calcium binding protein S100B in mice and biopsy samples from humans. This protein stimulates the pro-inflammatory cytokines interleukin-1β (IL-1β) and TNF-α (Bianchi et al., 2010) It was concluded that CBD treatment was able to reduce intestinal inflammation, and therefore reduce intestinal damage.

Borrelli et al. (2009) investigated the protective effects of CBD in a mouse model of colitis. In order to induce colitis, researchers administered dinitrobenzene (DNBS) in the colon of mice and analyzed the macroscopic and microscopic changes that occurred. In the experimental group, mice were given 5 mg/kg of CBD daily for 6 days, with the first injection occurring 3 days prior to the DNBS administration. Researchers measured body weight, intracellular ROS levels, endocannabinoid levels, and the cytokines IL-1β and interleukin-10

(IL-10) in order to measure the effects of CBD on colitis. Body weight loss, which commonly accompanies colitis, was attenuated in the CBD group. Concentrations of the pro-inflammatory IL-1β were significantly reduced. Concentrations of the anti-inflammatory IL-10 were increased in the experimental group. Endocannabinoid levels, which can be increased in humans with various forms of irritable bowel disease (Izzo & Camilleri, 2008), were elevated at baseline, but did not change after CBD treatment. Borrelli et al. (2009) concluded that the protective effects of CBD are not dependent on fatty acid amide hydrolase, an enzyme that hydrolyzes the endocannabinoid anandamide.

Pneumococcal meningitis, which affects the central nervous system, is a life-threatening disease that is characterized by an infection that elicits a large inflammatory response. The magnitude of this inflammatory response is proportional to the magnitude of severity that accompanies the disease (Täuber & Moser, 1999). Barichello et al. (2012) investigated the effects of CBD supplementation on inflammatory markers associated with pneumococcal meningitis in rats. Adult male Wistar rats were injected with a solution that induced pneumococcal meningitis. The rats were given either a single dose, or one dose daily for 9 days of CBD at varying concentrations (2.5, 5, and 10 mg/kg). The cytokines TNF-α, IL-6, and IL-1β, along with brain-derived neurotropic factor (BDNF), were measured following CBD administration via an intraperitoneal injection. A single injection, at any dose, was unable to blunt the increase associated with pneumococcal meningitis in the frontal cortex and hippocampus. In the group that received treatment daily for 9 days following the development of the disease, no differences were observed with cytokine concentrations in the hippocampus. A significant decrease in TNF-α, at all measured doses in the frontal cortex following 9 days of supplementation, was observed. Levels of BDNF were significantly increased versus the control

group following 9 days of CBD supplementation. Although the dosage was small (10 mg/kg), CBD may have some anti-inflammatory benefit (Barichello et al., 2012).

Patients with diabetes can experience cardiovascular complications. Diabetic cardiomyopathy is associated with high mortality rates in individuals diagnosed with diabetes (Regan et al., 1994). Rajesh et al. (2010) investigated the use of CBD in a mouse model of diabetic cardiomyopathy. Researchers measured blood sugar levels, cardiac function, oxidative stress, and the pro-inflammatory cytokine TNF-α in order to determine if CBD could have a potential therapeutic effect on mice with this condition. In the first set of experiments, diabetic mice were given varying doses of CBD (1, 10, or 20 mg/kg) via injection for 11 weeks. In the second set of experiments, mice were injected with CBD for 4 weeks following the development of diabetic cardiomyopathy. The difference in timing of administration was to determine if CBD is able to slow, or eliminate, the onset of the disease, or reduce the progression once the disease was induced. No significant interaction with CBD and blood glucose levels or insulin concentrations was observed in any of the groups. With regard to myocardial dysfunction, CBD was found to attenuate diastolic and systolic left ventricular function in both groups. In the diabetic mice that were treated for 11 weeks, CBD treatment was found to attenuate the steep rise in diabetic-induced myocardial oxidative stress. With regards to inflammation, researchers found that CBD was able to significantly decrease TNF-α levels in diabetic mice who were treated for 11 weeks. Researchers hypothesized that CBD is a potent inhibitor of pro-inflammatory pathways in microglia cells (Kozela et al., 2010).

Microglial cells are macrophages found in the central nervous system and act as a first line of defense against pathogens. When activated, these cells start a pro-inflammatory cascade and are critical to the neuroinflammatory process (Kozela et al., 2010). The effect of CBD on

microglial cells, and the subsequent inflammatory process, was researched by Kozela et al. (2010). Researchers utilized BV-2 cells *in vitro*. These cells exhibit morphologic and functional features comparable to microglial cells (Larson et al., 2010). The BV-2 cells were exposed to LPS in order to induce a pro-inflammatory response, as LPS has been shown to increase the secretion of IL-1β, IL-6, and interferon β, in microglial cells (Gay & Gangloff, 2007). Kozela et al. (2010) found that THC and CBD significantly, and dose-dependently, decreased the measures of IL-6 and IL-1β when taken in a 10 μM dose. The pro-inflammatory IL-1β was reduced by 54 ± 13% with THC, and 64 ± 9% with CBD. At a similar dosage, IL-6 was reduced by approximately 25% with THC, but was reduced 91 ± 1% with CBD (Kozela et al., 2010).

In the study by Kozela et al. (2010), the researchers also investigated two different pathways that LPS was known to activate. This was completed in order to examine the potential mechanism by which CBD and THC elicit an anti-inflammatory response. The first pathway, the factor 88 (MyD88)-adapter protein-dependent pathway, activates NF-κB-dependent transcription, leading to a pro-inflammatory response. The second pathway, the MyD88-independent pathway, is regulated by the toll-interleukin-1-receptor (TIR) and regulates cytokine release via signal transducers and activators of transcription (STAT)-dependent pathways. Once activated, STAT-dependent pathways induce the expression of pro- (STAT1) or anti- (STAT3) inflammatory genes (Wesoly et al., 2007). Kozela et al. (2010) found that CBD was effective with inhibiting the NF-κB signaling pathway, reducing the activation of pro-inflammatory STAT1, and increasing the activation of anti-inflammatory STAT3. Additionally, Kozela et al. (2010) hypothesized that the anti-inflammatory effects of CBD may not be purely through CB1 or CB2 receptors, but through a broad spectrum of endogenous signals which respond to cytotoxic changes in the body (Kozela et al., 2010).

Chronic inflammation of the airway is a primary cause of asthma, a disorder that is associated with bronchial hyperresponsiveness. Those with asthma typically possess high concentrations of pro-inflammatory cytokines (Holgate, 2008). Vuolo et al. (2015) investigated the potential anti-inflammatory benefits of CBD in rodents with asthma. Mice were injected with ovalbumin, on alternate days for 2 weeks, in order to induce an asthmatic state. The mice were then divided into three groups: control, a group that received 5 mg/kg of CBD, and a group that received 10 mg/kg. Researchers also divided the 10 mg/kg dosage group into three subgroups, categorized by which receptor agonist they received: CB1, CB2, or both. Treatment with CBD at 10 mg/kg was able to significantly reduce the inflammatory markers measured, including IL-4, IL-5, and IL-13. The significant decreases observed with these cytokines in the 10 mg/kg group were not significantly different in either the CB1 or CB2 blocked groups. When both CB1 and CB2 receptors were blocked, inflammatory markers were significantly higher than those observed in the control group. Therefore, the mechanism by which CBD elicits an anti-inflammatory response may not be through CB1 and CB2 receptors alone, but rather through an interaction between several pathways (Vuolo et al., 2015).

Stroke, the leading cause of permanent adult disability, can be categorized as either ischemic or hemorrhagic. Ischemic strokes, with a prevalence rate of 87%, are caused by a disruption of blood flow to the brain, while hemorrhagic strokes primarily occur due to the rupture of a blood vessel (Bigdeli, 2011). Following an ischemic stroke, there is a large influx of inflammatory cytokines, such as IL-1β and TNF-α. This influx of inflammatory cytokines during the ischemic cascade can lead to brain tissue damage and has long term health implications. Therefore, reducing this inflammatory response would be of great benefit for this population (Jin et al., 2010). Khaksar and Bigdeli (2017) investigated the effects of CBD on

infarct volume and inflammatory markers associated with an ischemic stroke. Investigators used rats and surgically induced an ischemic stroke in each rodent. The animals were divided into five groups based on the treatment they received: control, saline, 50 ng CBD, 100 ng CBD, or 200 ng CBD. Each animal was measured for infarct volume, TNFR1 and NF-κB expression, and infarct size (Khaskar & Bigdeli, 2017). The authors found that 100 and 200 ng of CBD was able to significantly reduce both infarct size and volume in rats. No significant differences between control and vehicle (saline) were observed in the 50-ng group. The researchers also found that there was a significant correlation in the 100 ng and 200 ng CBD groups between TFNR1, NF-κB, and infarct volume. It was concluded that the decrease in infarction volume may be related to expression of TFNR1 and NF-κB. As TNFR1 is closely linked to the secretion of TNF-α, it is an important factor in the inflammatory cascade. Reduction in its expression may therefore reduce inflammation. The expression of NF-κB induces an inflammatory response through the release of IL-1 and IL-6 when active. These pathways are vital in the inflammatory response and appear to be downregulated by CBD (Khaskar & Bigdeli, 2017).

The NF-κB pathway of transcription factors is considered a pro-inflammatory signaling pathway, as it is critical in the expression of inflammatory cytokines, chemokines, and adhesion molecules (Lawrence, 2009). Therefore, the deregulation of the NF-κB pathway may play a primary role in a number of inflammatory diseases, such as rheumatoid arthritis, irritable bowel disease, asthma, multiple sclerosis, and chronic obstructive pulmonary disease (Pai & Thomas, 2008). In skeletal muscle, NF-κB regulates several pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β), promotes skeletal muscle regeneration, and influences muscle atrophy (Li et al., 2008). According to recent research, NF-κB signaling is activated following intense resistance exercise (Vella et al., 2011). Since the activation of the NF-κB pathway may be a

regulator in the magnitude of the inflammatory response observed following exercise, inhibiting this pathway may reduce inflammation (Xiao & Ghosh, 2005).

One pathway that has been researched to reduce NF-κB signaling is the peroxisome proliferator-activated receptors (PPAR) pathway. These receptors are a group of ligand-activated receptor proteins that regulate the expression of genes (Zhang et al., 2014). Three PPAR isoforms have been identified (α, β, and γ) and exhibit tissue-specific activation (Bordet et al., 2006). Expressed in the skeletal muscle, PPAR-α is critical in the regulation of amino acid metabolism, fatty acid homeostasis, and the inflammatory response (Muoio et al. 2002). Activation of the PPAR-α isoform directly inhibits the NF-κB signaling pathway (Kersten et al., 2000). The activation of PPAR-α is the mechanism by which CBD reduces inflammation (Sun & Bennett, 2007). CBD supplementation increases levels of anandamide, which in turn activates the PPAR-α isoform and inhibits the NF-κB signaling pathway (Bouaboula et al., 2005).

Lafuente et al. (2011) had similar findings when investigating the neuroprotective benefits of CBD following acute hypoxia-ischemia (HI) in newborn pigs. Researchers utilized 1 to 3-day old pigs who were anesthetized and paralyzed by IV. Next, the carotid arteries were clamped to reduce the fraction of inspired oxygen by 8 to 10% for 20 minutes. At varying time points 15 to 240 minutes later, the piglets either received 0.1 mg/kg of CBD or a saline treatment. Researchers analyzed the piglets on a number of variables including a neurophysiological assessment, neurobehavioral activity, biochemical analysis, and a histological analysis (Lafuente et al. 2011). The electroencephalogram (EEG) amplitude in the controls recovered to 42% of baseline measures after 72 hrs following HI. Treatment with CBD was able to increase EEG amplitude to 82% of baseline measures. Neurobehavioral assessments were taken prior to the HI event with the use of a scale that measured mental status, behavior,

nerve activity, reflexes, and motor performance. All animals included in the study had normal scores. After HI, animals without CBD treatment experienced a 39% drop in the neurobehavioral scale score after 24 hrs, while the animals treated with CBD only saw a 15% reduction. Levels of TNF-α were measured 6 hrs after HI. The control group exhibited a 2-fold increase over baseline, while the animals treated with CBD exhibited similar levels to baseline. Lafuente et al. (2011) hypothesized that the neuroprotective effect observed with CBD treatment is related to the anti-inflammatory properties of CBD, as demonstrated by a significant decrease in TNF-α levels.

Extreme inflammation in the brain can lead to several devastating conditions such as endotoxic shock, which has mortality rates ranging from 40-70% of those infected (Russel, 2006). Lipopolysaccharides are abundant in the cell wall of gram-negative bacteria and promote a highly pro-inflammatory response (Ngkelo et al., 2012). In cases of endotoxic shock, LPS stimulation can lead to several complications. Ruiz-Valdepeñas et al. (2011) investigated the therapeutic benefits of CBD as a potential treatment to LPS-induced inflammation in the brain of mice. Researchers compared the vascular and inflammatory changes that occurred for 3 hrs after injection of LPS, LPS + CBD (3 mg/kg), and CBD alone (3 mg/kg). With regards to cerebral blood flow, CBD was able to attenuate the LPS-induced vasodilation significantly, which led to reduced blood flow in the mouse brain. Laser scanning micrographs were used to determine the permeability of the blood brain barrier, which typically exhibits hyperpermeability in cases of endotoxic shock. A reduction in this permeability of the blood brain barrier was observed in mice treated with CBD. With regards to makers of inflammation, CBD administration significantly reduced TNF-α levels when compared to levels in the control group, leading the

authors to conclude that CBD had an anti-inflammatory effect on LPS-induced inflammation (Ruiz-Valdepeñas et al., 2011).

Multiple sclerosis (MS) is an autoimmune disease that leads to the demyelination of the white matter of the brain and spinal cord (Trapp & Nave, 2008). Many of the current therapies used to treat MS are aimed at reducing chronic inflammation, which led Mecha et al. (2013) to investigate the potential benefit of CBD on markers of inflammation in a model of MS. Researchers used both an *in vitro* and *in vivo* mouse model to induce MS, and then administered either CBD or a sham treatment. Researchers also attempted to identify the mechanism by which CBD elicits an inflammatory response by characterizing the effects of A_{2A} receptors on CBD (Mecha et al., 2013). With regards to inflammatory markers, 5 mg/kg of CBD was able to significantly reduce the activation of vascular cell adhesion protein 1 (VCAM-1) both *in vitro* and *in vivo*. This signaling protein is activated by pro-inflammatory cytokines, including TNF-α. Reduced activation of VCAM-1 is an accurate indicator of a reduced state of inflammation. Therefore, CBD was effective at reducing inflammation associated with MS. Researchers also investigated the role of adenosine in the anti-inflammatory response to CBD by giving mice an A_{2A} receptor antagonist. When given this antagonist, the treatment with CBD had no effect on VCAM-1 activation when compared to the control group. Adenosine and the A_{2A} receptor may have important roles in the mechanism of delivery for CBD (Mecha et al., 2013).

Chemotherapy is effective in treating a variety of cancers. However, it is well known that some of the associated drugs can cause a number of side effects, including renal injury. Cisplatin is one of the most potent chemotherapy drugs available, but can cause renal dysfunction (Pan et al., 2009). These side effects, which researchers have termed Cisplatin-induced nephrotoxicity, are primarily due to a severe inflammatory response following treatment. Pan et al. (2009)

investigated the use of CBD in treating the strong side effects associated with Cisplatin in rodent models. Researchers monitored renal function, ROS activity, and the pro-inflammatory cytokines TNF-α and IL-1, following a daily dose of 10 mg/kg of CBD. Renal function was assessed by measuring creatinine and blood urea nitrogen levels. These markers were significantly decreased following CBD administration, indicating increased renal function. The cytokines TNF-α and IL-1 were also significantly reduced following treatment with CBD. The use of CBD may therefore be an effective anti-inflammatory supplement for those with cancer (Pan et al., 2009).

Cannabidiol as an Antioxidant

The therapeutic use of CBD as an antioxidant is a promising therapeutic approach. Oxidative stress is associated with a number of chronic conditions, including cardiovascular disease, kidney disease, neurodegenerative disease, macular degeneration, and cancer (Liguori et al., 2018) Hampson et al. (1998) found that CBD and Δ^9-THC were independently able to reduce oxidative stress in mice with an induced neurological disorder. Researchers measured glutamate, a neurotransmitter released during an ischemic episode that can stimulate neural receptors to increase intracellular calcium to a toxic level. Neurotoxicity and ROS, which induce cell death, were prevented with CBD and Δ^9-THC administration. Also, when CBD was isolated from Δ^9-tetrahydrocannabinol, it elicited the same antioxidant properties as butylhydroxytoluene, an effective antioxidant (Hampson et al., 1998).

Gallily et al. (2018) compared the anti-inflammatory effects of CBD and three common terpenoids found in the cannabis plant. Researchers used the zyomasan-induced inflammation technique on mice to compare the differences between administration of 5 mg/kg of CBD and 10 to 50 mg/kg of three terpenoids. Paw thickness and serum TNF-α levels were measured. The

antinociceptive effects of these substances was also measured by paw withdraw. Measurements for all three variables were taken at 2, 6, and 24 hrs post-injection. With regards to paw thickness, CBD was significantly lower than control and the terpenoid rich oils at all three dosages (10, 25, and 50 mg/kg) at each time point. Paw withdraw was also significantly different when compared to control at all three time points with CBD. Levels of TNF-α were only measured 24 hrs post injection. A significant reduction in this pro-inflammatory cytokine was observed only with the CBD group. When compared to the control group, 5 mg/kg of CBD reduced the level of TNF-α by 48%, while no significant differences were observed amongst the three terpenoid rich oils (Gallily et al., 2018).

In summary, the therapeutic benefit of CBD supplementation may be useful with a variety of conditions. Specifically, CBD supplementation may improve symptoms associated with epilepsy (Devinsky et al., 2016), Alzheimers disease (Cheng et al., 2014), and Dravets syndrome (Devinsky, Patel, Theile et al., 2018). The cardioprotective benefits of CBD supplementation have also led to some significant findings *in vivo* through a reduction in heart rate and blood pressure (Resstel et al., 2006), infarct size (Durst et al. 2007), and cardiac dysfunction (Rajesh et al., 2010). The positive effects of CBD are likely due to an ability to reduce neural inflammation and oxidative stress, likely through reducing microglial cell migration and inhibiting NF-κB signaling (Fernández-Ruiz et al., 2013). To date, limited research has been conducted on the effect of CBD supplementation on human skeletal muscle, yet supplement manufacturers are marketing the product for its ability to enhance recovery from exercise.

Exercise Induced Muscle Damage & Inflammation

An individual's response to exercise is directly related to the duration, intensity, and familiarity of the exercise protocol (Baird et al., 2012). An unfamiliar exercise at a similar intensity and duration elicits a larger disruption within the skeletal muscle when compared to a familiar exercise (Sorichter et al., 2006). Training status also appears to provide a protective effect against muscle disruption, as individuals who exhibit higher levels of physical fitness possess a lower magnitude response in muscle disruption following exercise (Vincent & Vincent, 1997). Following strenuous exercise, the body undergoes a number of inflammatory and immunological responses aimed at restoring optimal physiological function (Pyne, 1994). Armstrong (1986) describes these responses as a three-phase process: autogenic, inflammatory, and regenerative. The autogenic phase occurs 2 to 6 hrs after the initial stress, and is characterized by a decrease in muscle cell membrane volume, which initiates the inflammatory response. During the inflammatory phase, an influx of macrophages and phagocytes begin the repair process, which can last hours to days. The final stage of repair is called the regenerative phase, which is characterized as the period where the muscle fiber is repaired and restored to its normal condition. The regenerative phase can last days or weeks depending on the severity of the damage caused to the muscle (Armstrong, 1986).

Muscle damage following exercise can be characterized as structural changes in the muscle, leading to increased proteins and enzymes in the bloodstream, loss of strength and range-of-motion, and an increase in muscle soreness (Peake et al., 2005). These changes can lead to a decrease in physical performance capabilities for several days to weeks, depending on the severity of the damage to the muscle (Cheung et al., 2003). While the exact mechanism of this damage is still debated, there are several mechanisms that could be responsible, including

mechanical factors (e.g., tension and strain), disturbances in calcium homeostasis, the inflammatory response, and the synthesis of stress proteins (Clarkson & Sayers, 1999).

Muscle Damage, Inflammation, and Supplementation

The acute and chronic response to exercise is partially regulated by cytokines. Chronic low-grade inflammation has been associated with several conditions, such as type 2 diabetes, atherosclerosis, and metabolic syndrome (Petersen & Pedersen, 2005). Regular exercise may be an effective means of reducing chronic low-grade inflammation (Geffken et al., 2001). Inflammation following strenuous exercise is aimed at clearing unwanted particles from the damaged muscle in order to regenerate the damaged tissue (Clarkson & Hubal, 2002). The magnitude of this inflammatory response is directly related to the exercise modality, intensity, and duration, and the muscles involved. Circulating levels of pro-inflammatory and anti-inflammatory cytokines in the blood can therefore give researchers an insight to the body's response to an exercise session (Zaldivar, 2006).

Inflammation following exercise can have negative effects on repeated performance and recovery between bouts of exercise. There is a large market for supplements that aim to reduce exercised-induced muscle inflammation. Coenzyme Q_{10} (CoQ_{10}) has been used for many years as a health supplement aimed at reducing oxidative stress (Ochoa et al., 2005). Díaz-Castro et al. (2012) investigated the anti-inflammatory capabilities of CoQ_{10} following exercise and found some potential benefits. Participants in this study were male amateur distance runners who completed a 50-km trail run receiving either a CoQ_{10} supplement or a placebo for 2 days prior to the event. Concentrations of the pro-inflammatory markers TNF-α, IL-6, and interleukin-1ra (IL-1ra) were measured via blood samples prior to, and immediately following, the running event. Those who received the CoQ_{10} supplement exhibited a significant decrease in oxidative

stress markers and TNF-α levels following the running event. These results demonstrate that CoQ_{10} supplementation could have some anti-inflammatory benefit with regards to exercise-induced inflammation. Researchers hypothesized that the reduction in TNF-α is a result of its ability to inhibit the activation of NF-κB, which is critical to the inflammatory cascade (Díaz-Castro et al., 2012).

The anti-inflammatory benefits of Omega-3 fatty acid supplementation following eccentric exercise have also been investigated. Tartibian et al. (2011) recruited 45 untrained males to participate in a randomized double-blind study that included measures of inflammation following an eccentric exercise protocol. Researchers utilized a 40-minute stepping exercise to induce muscle damage in the participants. For 30 days prior to the exercise protocol, participants in the Omega-3 trial consumed 324 mg of eicosapentaenoic acid (EPA) and 216 mg of docosahexaenoic acid (DHA) daily. Blood was collected prior to supplementation, prior to exercise, immediately following exercise, and daily for 2 days following exercise. Researchers measured creatine kinase, myoglobin (Mb), and lactate dehydrogenase to determine muscle damage, and measured TNF-α, IL-6 and prostaglandin E_2 to assess inflammation. No significant differences between the groups with regards to the measured blood markers were found before exercise. Following exercise, participants in the Omega-3 trial exhibited a significant reduction in IL-6, prostaglandin E_2, TNF-α, creatine kinase, and Mb at the 24- and 48-hour time points. The researchers proposed that an increase in blood levels of EPA and DHA suppresses the production of arachidonic acid, which is a key modulator of inflammatory cytokines (Tartibian et al., 2011).

Reducing muscle damage following exercise has a practical benefit for athletes and the general population. Nakhostin-Roohi et al. (2008) investigated the potential benefit of 500 mg of

vitamin C in athletes. Participants in this double-blind study were placed in the control or vitamin C group and asked to run on a treadmill for 30 minutes at 75% VO_{2max}. Researchers measured blood marker concentrations of muscle damage and inflammation prior to, 2 hrs following, and 24 hrs following the running session. Blood levels of creatine kinase were found to be significantly different between the control and treatment groups at the 24-hour time point, but not significantly different at the 2-hour time point. Total circulating leukocyte count, IL-6, and cortisol levels in the blood were measured to determine inflammation. No significant differences were observed between the two groups at any timepoint with regards to measured markers of inflammation (Nakhostin-Roohi et al., 2008).

Hsu et al. (2005) investigated the potential benefit of ginseng supplementation following submaximal exercise. Participants in this double-blind crossover designed study either received 400 mg of ginseng daily or a placebo for 4 weeks. At the end of the 4 weeks, participants completed a treadmill running protocol that consisted of running at 80% VO_{2max} until volitional fatigue. Blood measures were taken at varying timepoints before, during, and after the running protocol. Blood was analyzed for creatine kinase and lactate dehydrogenase levels. At each timepoint, lactate dehydrogenase levels were significantly lower with ginseng supplementation when compared to placebo. Supplementation with ginseng led to significantly lower levels for creatine kinase at all measured timepoints (20, 40, 60, and 120 min) following the running session. The researchers hypothesized that the change in creatine kinase levels observed was due to the protective effect of ginseng on the muscle cell membrane (Hsu et al., 2005).

Similar results have also been noted with the use of branched-chain amino acid (BCAA) supplementation after prolonged exercise (Coombes & McNaughton, 2000). In one study, participants were given 12 g/day of BCAA's for 14 days. Participants then performed a cycling

exercise for 120 minutes at 70% VO_{2max}. Blood samples were collected immediately prior to and immediately following exercise. Additional samples were collected at 1 hr, 2 hrs, 3 hrs, 4 hrs, 1 day, 3 days, 5 days, and 7 days post-exercise. Serum levels of creatine kinase and lactate dehydrogenase were measured as a means of determining muscle damage. When compared to the control group, which received a placebo, participants that received the BCAA supplement had significantly lower lactate levels across all measured time points. Creatine kinase levels were also found to be lower in the experimental group at each timepoint from 2 hrs to 5 days. Researchers hypothesized this protective effect of BCAA supplementation was due to the increase in the anabolic response elicited by the supplement following exercise (Coombes & McNaughton, 2000).

Taurine, an amino acid, may protect against oxidative stress and act as an anti-inflammatory intermediate in the muscle (Zhang et al., 2004). da Silva et al. (2013) investigated the supplemental effects of taurine on makers of muscle damage following eccentric exercise. Twenty-one male participants were placed either in the placebo group or received a taurine supplement (50 mg/kg) for 14 days. At the end of the 14-day supplementation period, each participant underwent an exercise protocol that consisted of eccentric elbow flexion that elicited muscle damage. Blood markers of oxidative stress, muscle damage, and muscle inflammation were measured at 2, 4, and 7 days following the eccentric exercise protocol. Taurine supplementation decreased creatine kinase levels at each timepoint following the eccentric exercise protocol. Performance measures and markers of oxidative stress were also improved at varying timepoints following the eccentric exercise protocol. Therefore, taurine may pose some benefit in limiting muscle damage following exercise (da Silva et al., 2013).

Baty et al. (2007) found that a carbohydrate and protein supplement reduced markers of muscle damage following resistance training. Thirty-four male college-age participants were recruited to complete three sets of eight repetitions, or until volitional fatigue, on the high pull, leg curl, standing overhead press, leg extension, lat pull-down, leg press, and bench press. Participants in the experimental group consumed a carbohydrate (6.2%) and protein (1.5%) supplement at 30 minutes prior, immediately prior, halfway, and immediately following the exercise bout. The control group consumed an electrolyte and artificial sweetener beverage at the same time points. Those that consumed carbohydrate and protein supplement did not experience an increase in exercise performance over the control group, but some significant findings were observed. Cortisol levels were significantly higher in the control group 24 hrs post-exercise, and Mb levels were significantly elevated in the control group 6 hrs post-exercise. Creatine kinase levels in the control group were significantly elevated 24 hrs post-exercise when compared to the experimental group. Researchers hypothesized that an increase in insulin concentrations was responsible for the reduced muscle damage in the experimental group, as insulin is known to increase protein synthesis and enhance tissue repair (Baty et al., 2007).

Cockburn et al. (2010) gave participants a milk-based carbohydrate and protein supplement at 3 different time points around a bout of muscle-damaging eccentric exercise. Participants were placed in one of four groups (pre, post, 24 hrs, or control) and given the supplement either before, after, or 24 hrs following the muscle-damaging protocol. Researchers measured performance, perceived muscle soreness, and blood levels of creatine kinase at 24, 48, and 72 hrs following the exercise protocol. Consuming the milk-based carbohydrate and protein supplement following exercise had a positive effect on muscle soreness and measures of performance. While no significant differences were observed with creatine kinase between the

groups, the results neared significance. These results indicate that a milk-based carbohydrate and protein supplement, when consumed following exercise, could prove beneficial in reducing muscle damage and restoring performance (Cockburn et al., 2010).

Prolonged running can be very damaging to skeletal muscle, and is often used as the exercise modality in muscle-damaging studies. Knitter et al. (2000) utilized prolonged running to investigate the effects of a β-hydroxy-β-methylbutyrate (HMB) supplement on muscle damage. Positive effects on strength and endurance during exercise have been observed with HMB supplementation. Thirteen participants (five men and eight women) took part in the study, in which creatine kinase and lactate dehydrogenase levels in the blood were quantified to assess the severity of muscle damage. Participants in the experimental group completed 6 weeks of HMB supplementation prior to completing a maximal effort 20-km run. Blood samples were taken prior to, immediately following, and daily for 4 days following the 20-km run. Participants that received the HMB supplement had significantly lower blood levels of creatine kinase for each timepoint following the 20-km run when compared to a placebo. Lactate dehydrogenase levels were also significantly reduced at each measured timepoint following the run when compared to a placebo. Researchers hypothesized that the protective mechanism involved is due to the conversion of HMB to HMB-CoA, which serves as the pre-cursor for cholesterol synthesis and supports cell membrane integrity (Knitter et al., 2000).

A significant amount of research has been conducted with the supplemental use of creatine phosphate and its potential for performance enhancing capabilities. While results of this research are mixed, creatine phosphate is the one of the most popular exercise related supplements (Cooper et al., 2012). The supplement may have a potential benefit with regards to muscular strength and repeated sprint endurance, but little research has included the use of

creatine supplementation as recovery aid following strenuous exercise. The potential anti-inflammatory use of creatine was investigated by Deminice et al. (2013), who measured oxidative stress and inflammatory markers following repeated sprint exercise in 25 soccer players. Participants in the experimental group received creatine supplementation for 7 days (0.3 g/kg) and completed a repeated sprint test prior to, and at the end of, the 7-day supplementation. Blood samples were taken immediately prior to, at the completion of, and 1 hr following each sprint test. Those who supplemented with creatine were able to significantly attenuate the increases in C-reactive protein (CRP) and TNF-α. These increases were observed without supplementation. No differences in oxidative stress markers were noted after 7 days of creatine use. The authors hypothesized that the anti-inflammatory effect of creatine phosphate was due to an increase in intracellular levels of creatine, which aid in adenosine triphosphate (ATP) production and can elicit a decrease in inflammatory activity through the adensosine-A_{2A} receptor (Deminice et al., 2013).

The anti-inflammatory properties of some natural foods have been well researched, with strong evidence supporting their benefit (Yuan et al., 2006). The use of blueberries as an antioxidant and an anti-inflammatory supplement following strenuous exercise is promising. McAnulty et al. (2011) researched the use of blueberries in combatting inflammatory and oxidative responses following 2.5 hrs of running in human participants. Members of the experimental group consumed 250 g/day of blueberries for 6 weeks in addition to their normal diet, while members of the control group maintained normal eating habits. Researchers collected blood samples and a muscle biopsy one hour prior to, and one hour following, the run. The exercise intensity was maintained at 72% VO_{2max}. While no differences in running performance were observed between the groups, plasma levels of the anti-inflammatory cytokine IL-10 were

significantly higher in the group that consumed blueberries. Researchers found no differences between the groups with regard to measured pro-inflammatory cytokines (i.e., IL-1ra, IL-6, and IL-8), and no changes in skeletal muscle NF-κB activity were reported. The researchers were unclear how blueberries could increase IL-10 blood plasma levels (McAnulty et al., 2011).

In a similar study, Bell et al. (2014) found significant results with Montmorency cherry supplementation following strenuous cycling. Well-trained cyclists (average VO_{2peak} of 61.6 ml/kg/min) consumed 30 ml of Montmorency cherry concentrate twice daily for 8 days prior to completing a 109-min strenuous cycling activity. Blood samples were taken immediately prior to, immediately following, and 1, 3, 5, 24, 48, and 72 hrs following the cycling challenge. Samples were analyzed for measures of inflammation, muscle damage, high-sensitivity CRP, and oxidative stress. Researchers found that the participants who consumed the Montmorency cherry concentrate exhibited a significant attenuation of IL-6 and CRP at the 24-hour post exercise time point. No differences were observed in performance, muscle damage, or makers of oxidative stress. The authors conclude that the Montmorency cherry supplementation had a positive effect on inflammation following strenuous cycling (Bell et al., 2014)

Cannabidiol and Exercise-Induced Muscle Damage

Recently researchers have begun to investigate the effects of CBD supplementation following strenuous exercise in human participants. In a study investigating subjective soreness measures and performance, researchers found that 150 mg of CBD oil taken immediately following, and 24 and 48 hrs following muscle damage was unable to reduce subjective feelings of soreness or restore performance compared to a placebo treatment (Cochrane-Snyman et al., 2021). Participants in this study (n = 13) were untrained males who completed six sets of 10 repetitions of eccentric elbow extensions to induce muscle damage. Peak torque, subjective

measures of soreness, and arm circumference were recorded immediately following, 24, and 48 hrs after the muscle damaging session with no condition-time interaction found between the treatment groups (Cochrane-Snyman et al., 2021). These results suggest that 150 mg of CBD oil is unable to reduce soreness or restore performance following strenuous exercise.

In a similar study, Isenmann et al. (2021) elicited muscle damage using a back squat and depth jump protocol and supplied participants either 60 mg of CBD or a placebo immediately after. One-repetition maximum in the back squat, countermovement jump, and blood serum concentrations of creatine kinase and Mb were measured at 24, 48, and 72 hrs in 16 participants. CBD supplementation was given immediately following the muscle damaging protocol and was administered via a 60 mg CBD solubilisat with water. Results of the study found no significant differences between treatment groups at the 24 and 48 hr timepoints for any of the measured variables. However, at the 72 hr timepoint serum measures of creatine kinase and Mb were significantly lower in the CBD group indicating a reduction in blood markers of muscle damage. This reduction in serum markers of muscle damage at the 72 hr timepoint indicates that CBD may play a protective effect on the muscle when given immediately following exercise (Isenman et al., 2021).

CBD supplementation has recently been shown to decrease subjective measures of fatigue. Hatchett et al. (2020) found that 16.67 mg of CBD when given with 1 ml medium-chain triglyceride (MCT) oil was able to reduce subjective fatigue when compared to a placebo treatment. Twenty-three untrained participants completed four sets of 10 repetitions of eccentric back squat and were given either a placebo, MCT oil, or CBD and MCT oil. Results of the study found that at 24, 48, and 72 hrs following muscle damage, the participants that consumed CBD and MCT oil had significantly lower scores of fatigue as reported on a visual analogue scale

(Hatchett et al., 2020). These results, in addition to Isenmann et al.'s (2021) findings suggest a potential benefit from taking CBD following intense exercise yet neither researcher hypothesizes on the specific mechanism by which this benefit could occur.

Heart Rate Variability

The autonomic nervous system innervates the heart and regulates heart rate. The balance between the parasympathetic and sympathetic nervous system affects the consistency in time between heart beats. This time between beats can be measured and is referred to as heart rate variability (HRV). Autonomic regulation of the cardiovascular system as measured by HRV is an accurate indicator of several performance measures, such as: a) training adaptation, b) increased performance, and c) fatigue (Vesterinen, et al., 2013). HRV can be a beneficial tool for athletes and coaches in monitoring an individual's physiological readiness to train. An increased HRV, or an increase the in variability of time between beats, indicates a higher parasympathetic tone and a better readiness to train (Plews et al., 2013). Training guided by HRV elicits a significant benefit in performance measures (e.g., VO_{2peak}, maximum workload) when compared to a traditional training plan in moderately active runners (Kiviniemi et al., 2010). For the purposes of this research, HRV was collected in an attempt to determine if autonomic regulation of heart rate had a significant relationship with markers of muscle damage following eccentric exercise-induced muscle damage.

Visual Analog Fatigue Scale

Measuring fatigue in exercising participants can allow researchers and coaches to be aware of the participant or athlete's perceived fatigue. One effective way of accurately measuring fatigue is with the use of a visual analog fatigue scale (VAFS). One version of this scale utilizes a vertical 10 cm line with the bottom of the line representing *no fatigue*, while the

top of the line represents *very severe fatigue*. Individuals are asked to draw a horizontal line across the vertical line indicating the level of fatigue they feel between *no fatigue* and *very severe fatigue*. In order to score the scale, researchers measure the vertical distance between the bottom of the line in millimeters and record that number as the score. With this scale, a higher number represents a more fatigued state. Tseng et al. (2010) found the VAFS to be a reliable and valid measure of exertional fatigue in exercising participants.

Summary

The use of CBD to treat clinical conditions such as pain, inflammation, epilepsy, and multiple sclerosis has proven effective (Bruni et al., 2018). CBD supplementation has shown to be tolerable at high doses with minimal side effects documented through research (Iffland & Grotenhermen, 2017). Currently, there is a large increase in the availability and marketing of CBD products. According to Leas et al. (2019) a 605% increase in Google searches of the term "CBD" in 2019 has been recorded, when compared to 2014. According to the researchers, the phrase "CBD" was searched more than the term "exercise" in 2018 (Leas et al., 2019). The growth in the popularity of CBD has yielded a wide range of research, primarily focusing on clinical conditions. To date, there is limited research on CBD and exercise, and no published research has investigated any effects of CBD supplementation with regards to inflammation following exercise. It is the objective of the researchers to begin to identify what effects, if any, CBD supplementation has on recovery measures from strenuous exercise.

CHAPTER III

METHODS

Experimental Approach to the Problem

To examine the effects of CBD on markers of muscle damage, inflammation, and performance, a double-blind, placebo-controlled, repeated-measures, crossover design was utilized. Twenty-seven female athletes consumed 5 mg/kg bodyweight of CBD and a matched weight of the placebo orally via pill form (i.e., treatment). Participants performed two muscle damaging sessions separated by approximately 28 days. Blood was collected 2 hrs prior to, and 4, 24, and 48 hrs following the completion of a muscle damaging protocol (i.e., trial). All blood samples were measured for Mb, IL-6, IL-10, and IL-1β. Participants performed five measures of performance immediately prior to, and 4, 24, and 48 hrs following completion of the muscle damaging protocol in an effort to determine the magnitude of performance loss.

Participants

Twenty-seven female participants were recruited using a convenience sampling technique. Using word-of-mouth and email, participants were recruited from Texas Woman's University and the University of North Texas. Participants were screened to include those who: 1) were current or previously NCAA Division I or II female athletes that have participated in a structured strength and conditioning program for a minimum of 6 months, 2) were in the off-season portion of their competitive sport if current athletes, 3) were 18-26 years of age, 4) were deemed healthy as determined by a medical questionnaire and PAR Q+ questionnaire, and 5) had the ability to follow verbal directions.

Participants were also screened to include those without: 1) musculoskeletal injuries within the previous 30 days that limited the ability to train, 2) orthopedic problems that could be

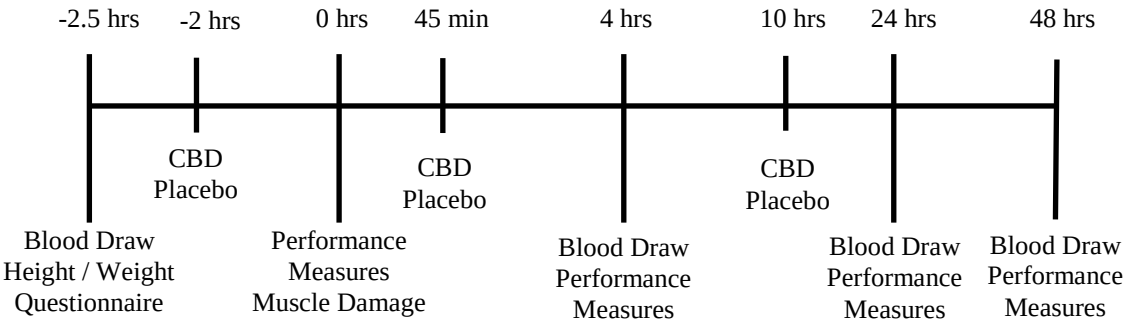
exacerbated by exercise, 3) known cardiovascular issues that may affect HRV or preclude them from exercise, 4) consumption of any Cannabis product or byproduct in the previous 30 days, 5) consumption of anti-inflammatory medication for the previous 48 hrs, 6) chronic exposure to, or consumption of, nicotine products within 48 hrs, and 7) consumption of any alcohol within the 48 hrs prior to beginning the each trial.

Study Protocol

The experimental study design for each treatment (CBD and placebo) is outlined in Figure 1. A double-blind, placebo-controlled, repeated-measures, crossover design was utilized to determine if differences existed among the participants with regards to markers of muscle damage, inflammation, and performance. Participants completed six visits in total, with Visits 1 and 4 consisting of blood collection, performance measurements, and a muscle damaging protocol. Visits 2, 3, 5, and 6 involved blood collection and performance measures only. Following recruitment, researchers ensured each participant met the inclusion criteria. Once the medical questionnaire and informed consent had been completed, participants entered the study. Researchers randomized the treatment each participant received first, as well as the leg the participants used for each treatment using the research randomizer website (www.randomizer.org). Once randomly assigned to a treatment group, participants notified the researchers upon onset of menses, at which point the first trial began within 7 days. A washout period of approximately 4 weeks was completed to allow for standardization of the menstrual phase and to ensure complete recovery from the muscle damaging protocol. Participants were required to comply with all exclusion criteria in the period between Visits 3 and 4. Participants were informed that they could potentially receive the same treatment for each trial in order to prevent them from anticipating treatment conditions.

Figure 1

Study Timeline for Given Treatment



Visits 1 and 4: Muscle Damaging Sessions

For muscle damaging sessions, participants reported to the laboratory at approximately 07:00 for each session following an 10 hr fast (water only, no caffeine) and had performed no strenuous physical activity for 72 hrs prior. Participants were measured for weight (kg) using a digital scale (Tanita BWB-800, Arlington Heights, IL) and height (cm) using a stadiometer (Perspective Enterprises Model PE-AIM-101; Visit 1 only). A blood sample was collected. Participants then orally consumed the appropriate treatment, either 5 mg/kg of CBD or a placebo, and researchers noted the time in order to begin the muscle damaging session 2 hrs following consumption of the treatment. All participants consumed a standard snack following blood collection consisting of 4 kcal/kg of body weight (Clif Bar & Company, Emeryville, CA; 250 kcal per 68 g serving; 18% fat, 68% carbohydrate, 14% protein). Participants were then free to leave the laboratory and reported back 2 hrs following consumption of the treatment, or at approximately 09:30. Participants were instructed to refrain from ingesting anything other than water or participating in physical activity outside of walking during this period.

Performance Measures

Upon returning to the lab, participants completed a 10-min warm-up at a self-selected cadence, maintaining heart rate (HR) under 60% of their age-predicted maximum HR ([206.9-(0.67 x age)]; Tanaka et al., 2001) on an electronically braked cycle ergometer (Ergomedic 828E; Monark Exercise AB, Vansbro, Sweden). After completing the 10-min warm-up, participants completed a countermovement vertical jump test utilizing a Just Jump mat (Probotics, Huntsville, AL). All participants were allowed five submaximal warm-up vertical jumps with 30 seconds of rest between jumps prior to beginning the test. Participants stepped on the mat and placed their feet at hip width. Participants performed three maximum effort jumps with 1 min of rest between each repetition. Participants highest of the three maximum effort jumps was recorded to the nearest tenth of a cm.

All strength testing and the muscle damaging protocol was implemented using a Biodex System-3 isokinetic dynamometer (Biodex Medical Systems, Inc., NY, USA). For all measures collected, the seat orientation was 90° and the seatback tilt was set to 80°. To familiarize themselves with the dynamometer, participants were allowed five repetitions at each speed at 50% of perceived maximal effort at each of the three tested speeds. In order to measure dynamic strength of the knee extensors, participants completed 10 maximal unilateral concentric-concentric repetitions at 60°, 180°, and 300°/sec. The range of motion for the dynamic strength test started at 0° of knee flexion and ended at 90° of knee flexion. One minute of rest was given between each set, with the researchers recording peak torque (N · m) for the concentric knee extension at each speed for analysis.

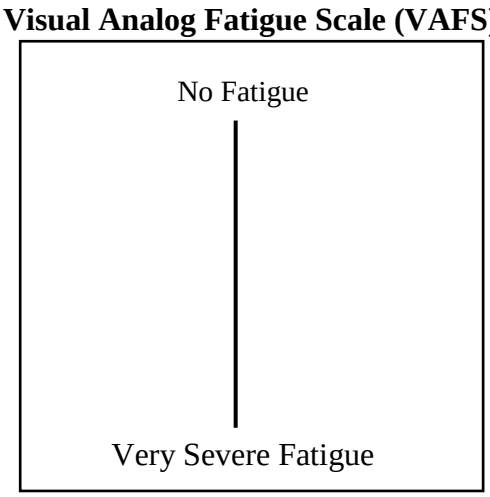
After a 3-minute recovery period, participants completed the isometric strength test on the dynamometer. Using the knee extensor of the leg chosen through random group assignment,

participants produced a total of three maximal voluntary contractions for 5 sec each, with one minute of rest between each repetition. For isometric strength testing, the knee angle was set at 90° of knee flexion with the lateral femoral epicondyle aligned with the axis of the dynamometer. Participants highest peak torque (N · m) exerted across the 3 trials was recorded for analysis. Participants completed a 5-min rest period before beginning the muscle damaging protocol.

Following the performance measures, participants completed the VAFS. The VAFS is a vertical 10-cm line with the top of the line representing *no fatigue*, while the bottom of the line represents *very severe fatigue*. Individuals were asked to draw a horizontal line across the vertical line indicating the level of fatigue they feel between *no fatigue* and *very severe fatigue*. Researchers then measured the vertical distance between the top of the scale and the line drawn by participants in millimeters, and recorded that number as the score. A visual representation of the VAFS is in Figure 2.

Figure 2

Visual Analogue Fatigue Scale (VAFS)



Muscle Damaging Protocol

The muscle damaging exercise protocol consisted of 10 sets of 10 repetitions of eccentric leg extensions. A similar protocol has been proven to elicit a sufficient muscle damaging and inflammatory response (Willoughby et al., 2003). All repetitions were completed at an isokinetic speed of 30°/sec on the dynamometer. Each repetition began at 0° of knee flexion and ended at 80° of knee flexion with a torque threshold of 300 ft-lbs. For all repetitions, no concentric effort was exerted by the participants. Participants completed each set with no more than 3 sec of rest between repetitions, with 1 min of complete rest given following each set. After completing the muscle damaging protocol, participants were free to leave the laboratory for 3.5 hrs and resume their normal daily nutritional habits.

Blood Collection

Blood samples were collected at 2.5 hrs prior to, and 4, 24 and 48 hrs following muscle damaging protocol for each treatment. Each blood sample, excluding the 4-hr post muscle damaging sample, was performed following an 10-hr fast (water only, no caffeine). For each blood sample, 10 mL of blood was collected via venipuncture from the antecubital vein in a normal clotting tube (SST II Advance, BD Biosciences). Researchers alternated arms for each successive blood draw. All samples were centrifuged after 30 min (1500 g, 10 min, 4° C), and serum was stored at -80° C until further analysis.

Supplementation

Upon completion of the initial (-2.5 hrs) blood collection, researchers supplied the participants with 5 mg/kg of CBD (Cannabidiol Life, Longwood, FL) or a matched weight of the placebo (microcrystalline cellulose powder, Bulk Supplements, Henderson, NV), orally via pill

form. The same treatment was given to the participants immediately following completion of the muscle damaging protocol. Participants were then provided with the appropriate treatment and instructed to consume the supplement 10 hrs following the muscle damaging protocol. For each treatment, participants were asked to maintain regular nutritional habits until completion of the 48-hr follow-up visit.

Both the placebo and CBD supplementation preparation were handled by the primary researcher. After treatments were prepared they were provided to a secondary researcher who was responsible for randomizing treatment order and then dispensing the correct treatment to participants. Both treatments were in powder form and put into identical Solaray vegetarian size 00 capsules (Nutraceutical, Salt Lake City, UT). The placebo capsules were matched in weight to the treatment capsules. Treatments were measured, prepared, and labeled in a plastic bag by the primary researcher. In order to blind the primary researcher, a secondary researcher removed each treatment out of the bag and placed them in an opaque plastic container with a lid. The containers were then labeled as "Treatment #1" or "Treatment #2."

Visits 2, 3, 5 and 6: Performance Measure Sessions

Participants returned to the laboratory 24 and 48 hrs following each muscle damaging protocol in a fasted state (10 hrs, water only, no caffeine). Blood was collected upon arrival, and participants were supplied with the snack as they were in Visits 1 and 4. Participants then began the same 10-min warm-up as the muscle damaging session. After completing the warm-up, static vertical jump was performed, and dynamic and isometric strength was assessed as outlined in the muscle damaging sessions. Approximately 28 days separated Visit 3 with Visit 4, with Visit 4 occurring within the early follicular phase (Days 2-7 after the start of menses).

Heart Rate Variability

HRV was recorded with the use of a Polar H7 heart rate monitor (Polar OY, Finland). HRV was collected immediately upon awakening in the morning for each trial. Researchers used the Elite HRV smartphone application (Elite HRV LLC, Asheville, NC, USA) to collect and analyze HRV data. Each HRV recording was 2 min in length, during which time participants were instructed to maintain a respiration rate of 12-18 breaths per minute using the metronome function of the application. For each recording, researchers recorded the root mean square of successive RR interval differences (RMSSD). Researchers educated the participants on how to use the app prior to the first data collection day.

Biochemical Analysis

Concentrations of IL-6, IL-10, and IL-1β were analyzed with the MILLIPLEX® Map Human High Sensitivity T Cell assay using a custom bead panel kit (EMD Millipore Corporation, Bellerica, MA, USA). The analysis followed the manufacturer's instructions for preparation and execution of testing. Concentrations of Mb were analyzed with an Abnova MB (Human) ELISA kit (Abnova, Taipei, Taiwan). Researchers followed the manufacturer's instructions for all procedures, and all measures were performed in duplicate. Inter-assay and intra-assay coefficients of variation (standard deviation / mean) were reported. Measured serum values found within expected normal physiological reference interval were recorded as the average of the duplicate results. Values that fell outside of expected physiological reference interval were removed as outliers and the single measure within range was recorded.

Statistical Analysis

An *a priori* power analysis was conducted using statistical software (G*power 3.1.9.2, Dusseldorf, Germany) to determine the minimum sample size required to find statistical

significance. With a desired level of power at .80, an alpha (α) level at .05, and a moderate effect size of .25 (f), it was determined that 24 participants would be required (Cohen, 2013). A moderate effect size was chosen based on findings from previous unpublished research in our laboratory in which HRV and performance measures were assessed following tailored exercise programming. Statistics software (IBM SPSS Statistics v.24, Armonk, NY) was used to analyze all data for performance, VAFS, and blood markers. First, a repeated-measures analysis of variance (RM ANOVA) was conducted to determine any differences in Mb and VAFS between groups and across the four timepoints (trials). Principle component analysis (PCA) was utilized to create a composite score at each trial for the five performance measures (concentric peak torque at 60°, 180°, and 300°/s, maximum peak isometric torque, and maximum vertical jump height). Using dimension reduction through factor analysis, one composite score for each treatment and trial was created which represented all measured performance variables. Results of the PCA were unable to extract a strong composite score, therefore a repeated measures multivariate analysis of variance (RM MANOVA) was performed. Due to this procedure being omnibus, *post hoc* analysis was needed to determine significant differences in treatment, trial, and treatment/trial interaction. Researchers performed a univariate RM ANOVA for all dependent variables after significant interactions were found with regards to trial. All significant interactions found between measured variables were analyzed using a *post hoc* Šídák test. Significance for all statistical analysis was set at 0.05. An RM MANOVA was used to examine potential differences in treatments with regard to inflammatory markers. To expand on previous research, the relationship between HRV and muscle damage was examined. A repeated measures correlation coefficient was conducted between measured HRV and Mb levels across all

trials with the placebo treatment using RStudio rmcorr R package. Data were analyzed for outliers using a Grubbs' test with identified outliers being removed for data analysis.

CHAPTER IV

RESULTS

Participant Characteristics

Twenty-seven female NCAA athletes were recruited and signed a university-approved informed consent form. Twenty-four participants completed all procedures. Two participants withdrew due to relocation following graduation. Venipuncture was not possible on another participant due to inaccessibility of vessels. All participants responded favorably to the treatment dose with no adverse reactions reported across all participants. Descriptive characteristics of participants who completed all required sessions of the study (n = 24) are outlined in Table 1.

Table 1

Descriptive Characteristics of Participants

Characteristics	Values
Age (yrs)	21.2 ± 1.8
Height (cm)	166.4 ± 8.0
Weight (kg)	64.9 ± 9.1
BMI (kg/m^2)	23.7 ± 2.4
Vertical Jump Performance (cm)	49.3 ± 8.1

Note. Values are presented as mean ± SD; yrs = years, BMI = Body Mass Index, calculated as Body Mass (kg) / Height (m^2).

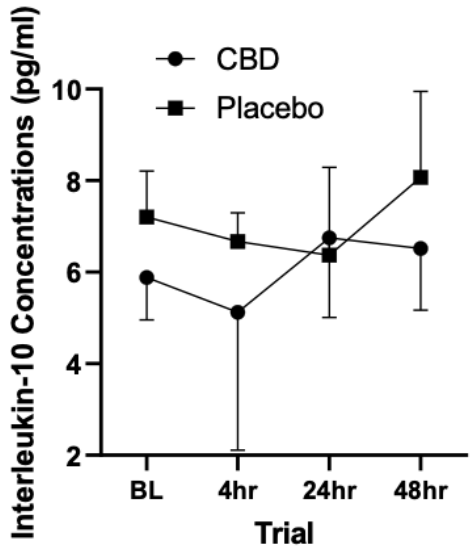
Inflammatory Response

In total, 86 of the 576 data points for inflammatory markers were not obtained at the time of analysis. Specifically, 26 data points were not obtained for IL-10, six data points were not obtained for IL-1β, and 54 data points were not obtained for IL-6. No significant differences (p = 0.573) were observed between the placebo and CBD treatments across the four measured trials.

Additionally, no significant differences (p = 0.337) were observed between the four trials with both treatments combined. Inflammatory markers can be seen in Figures 3, 4, and 5. Coefficient of variation values for inflammatory markers can be seen in Table 2.

Figure 3

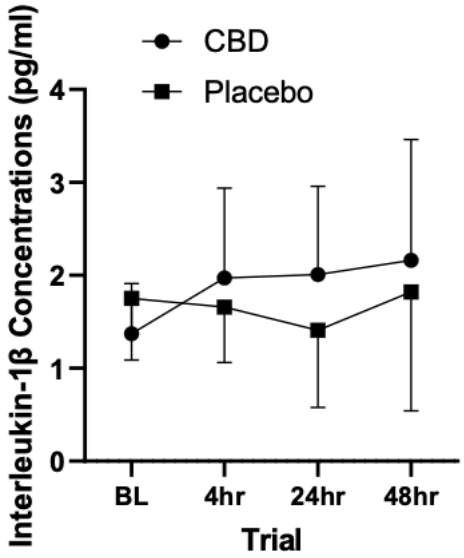
Interleukin-10 Concentrations



Note. BL = 2 hrs prior to muscle damaging protocol, 4hr = 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

Figure 4

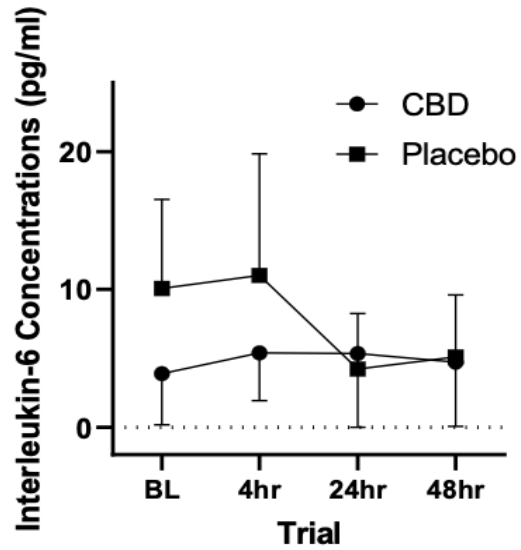
Interleukin-1β Concentrations



Note. BL = 2 hrs prior to muscle damaging protocol, 4hr = 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

Figure 5

Interleukin-6 Concentrations



Note. BL = 2 hrs prior to muscle damaging protocol, 4hr = 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

Table 2

Coefficient of Variation for Inflammatory Markers

Interleukin - 1β	Placebo	CBD
Pre	37.71%	39.42%
4-Hrs Post	36.14%	49.24%
24 Hrs Post	58.87%	47.26%
48-Hrs Post	70.33%	60.19%
Interleukin - 6	Placebo	CBD
Pre	64.15%	95.62%
4-Hrs Post	80.20%	64.19%
24 Hrs Post	95.50%	100.00%
48-Hrs Post	88.61%	98.94%
Interleukin - 10	Placebo	CBD
Pre	14.03%	15.65%
4-Hrs Post	9.45%	58.79%
24 Hrs Post	30.14%	25.78%
48-Hrs Post	23.30%	20.71%

Note. Values calculated as (standard deviation / mean)*100

Performance Measures

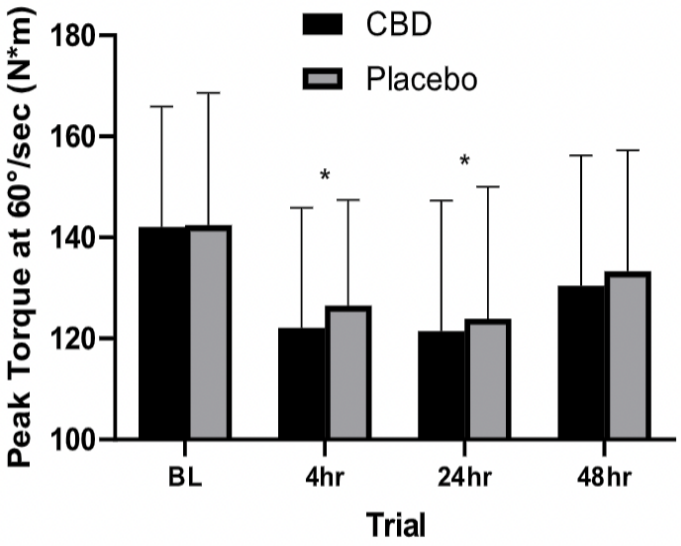
Based on the results of the PCA, a strong component (i.e., explained variance of composite score = 65%) could not be extrapolated, therefore an RM MANOVA was performed. No significant differences between the CBD and placebo treatments for dynamic strength at 60° (p = 0.479), 180° (p = 0.426), and 300°/sec (p = 0.927), isometric strength (p = 0.671), and vertical jump (p = 0.806) were observed across all trials. Significant differences were found between trials (p = 0.034) with treatments combined. Therefore, a *post hoc* RM ANOVA was performed to determine which specific performance measures differed between the 4 trials.

Based on the results of the RM ANOVA with a *post hoc* Šídák adjustment, 60°/sec peak torque and 5-sec peak isometric torque were significantly lower than baseline (i.e., 2 hrs pre muscle damage) measures between trials. Compared to baseline measurements, 60°/sec peak

torque was significantly reduced at 4- (p = 0.003) and 24-hrs (p = 0.001) following the muscle damaging session. Differences in 60°/sec peak torque between trials can be seen in Figure 6. With regards to 5-sec peak isometric torque, performance was found to be significantly reduced at 4- (p = 0.034) and 24-hrs (p = 0.023) following the muscle damaging session. Changes in 5-sec peak torque between trials can be seen in Figure 7. Data for all other performance measures can be found in Table 3.

Figure 6

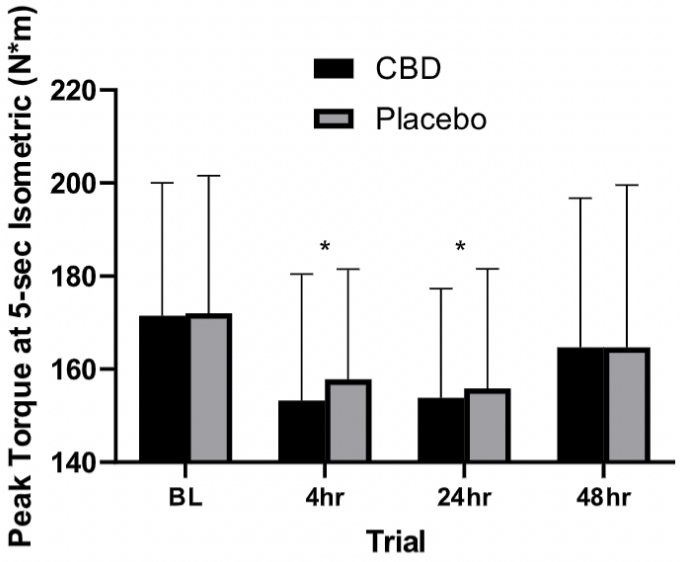
Peak Torque for 60°/sec Dynamic Strength



Note. * = statistically significant difference (p < .05) observed from baseline measurement. BL = 2 hrs prior to muscle damaging protocol, 4hr = 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

Figure 7

5-sec Peak Torque Measurements



Note. * = statistically significant difference ($p < .05$) observed from baseline measurement. BL = 2 hrs prior to muscle damaging protocol, 4hr= 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

Table 3

Performance Values

180º/sec - Peak Torque (N·m)	Placebo	CBD	*P* value
Baseline	101.9 ± 19.3	100.7 ± 21.1	
4-Hrs Post	92.2 ± 17.9	96.1 ± 21.7	0.410
24 Hrs Post	92.2 ± 18.9	97 ± 20.9	0.572
48-Hrs Post	99.3 ± 16.5	101.2 ± 22.8	0.999
300º/sec - Peak Torque (N·m)	Placebo	CBD	*P* value
Baseline	79.4 ± 14.4	79.7 ± 17.0	
4-Hrs Post	73.1 ± 14.4	75.4 ± 16.4	0.518
24 Hrs Post	75.4 ± 15.2	74.6 ± 17.0	0.689
48-Hrs Post	77.6 ± 14.4	76.6 ± 19.9	0.978
Vertical Jump (cm)	Placebo	CBD	*P* value
Baseline	48.6 ± 8.1	47.8 ± 7.9	
4-Hrs Post	45.3 ± 9.3	45.6 ± 7.4	0.423
24 Hrs Post	45.9 ± 7.2	45.6 ± 7.7	0.552
48-Hrs Post	47.3 ± 7.4	46.9 ± 7.3	0.979

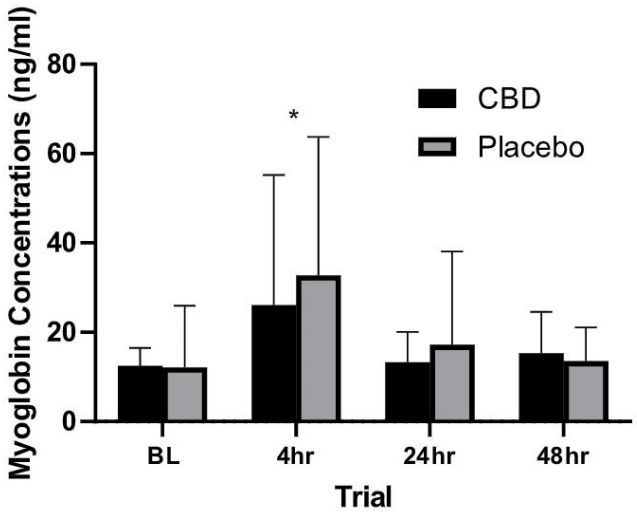
Note. Results are documented as mean ± SD.

Myoglobin

When both treatments were combined, a significant ($p = 0.002$) rise over baseline values in Mb levels was observed at the 4-hr timepoint (see Figure 8). Based on the results of the RM ANOVA, no significant differences ($p = 0.116$) were observed between placebo and CBD treatments across all trials. Coefficient of variation values for Mb measures can be seen in Table 4.

Figure 8

Myoglobin Values



Note. * = statistically significant difference (p = .002) observed from baseline measurement. BL = 2 hrs prior to muscle damaging protocol, 4hr = 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

Table 4

Coefficient of Variation for Myoglobin Concentrations

	Placebo	CBD
Pre	113.49%	31.94%
4-Hrs Post	94.53%	111.65%
24 Hrs Post	121.17%	50.78%
48-Hrs Post	55.44%	59.92%

Note. Values calculated as (standard deviation / mean)*100.

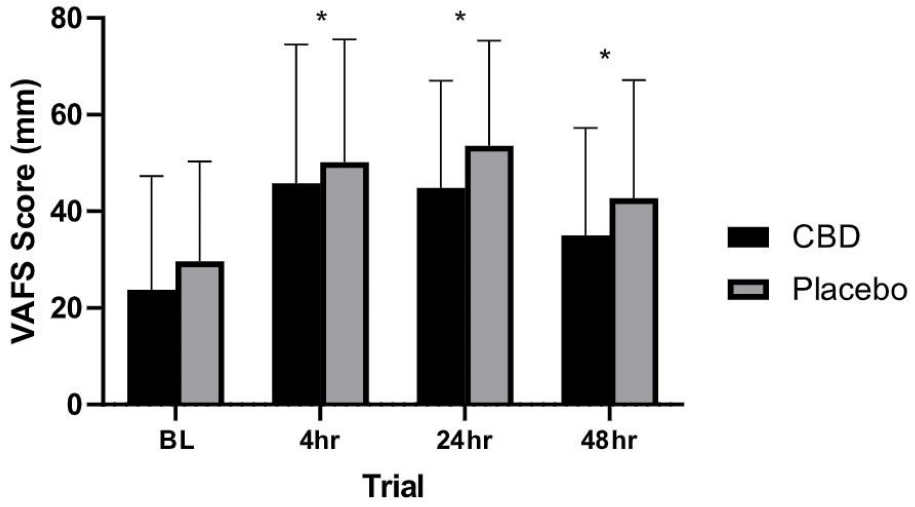
Visual Analogue Fatigue Scale

No significant differences (p = 0.126) for results on the VAFS were observed between the CBD and placebo treatments across all trials. Significant differences were observed between

the 4 trials when treatments were combined. Following the baseline measurement, a significant ($p < 0.001, < 0.001, = 0.01$) increase in the VAFS score was observed at 4, 24, and 48 hrs following muscle damage (see Figure 9).

Figure 9

Visual Analog Fatigue Scale Scores



Note. * = statistically significant difference ($p < .05$) observed from baseline measurement. BL = 2 hrs prior to muscle damaging protocol, 4hr = 4 hrs post muscle damaging protocol, 24hr = 24 hrs post muscle damaging protocol, 48hr = 48 hrs post muscle damaging protocol.

HRV and Muscle Damage

Due to a possible interaction between Mb and CBD, only HRV values collected for the placebo trial were analyzed. Of the 72 possible HRV measurements, 67 were successfully obtained. Some participants ($n = 3$) forgot to collect the data and others ($n = 2$) had technical difficulties with the device. A repeated measures correlation coefficient was computed to assess

the relationship between HRV values and serum Mb levels across trials with the placebo treatment. There was a weak (r = 0.10) positive correlation between HRV and Mb.

CHAPTER V

DISCUSSION AND SUMMARY

The purpose of this study was to investigate the effectiveness of CBD supplementation at reducing the markers of fatigue, loss of performance, and inflammation following intense eccentric exercise. CBD supplementation was unable to decrease markers of muscle damage, and subjective measures of fatigue, among these participants. Furthermore, return of performance to baseline measures was not expedited, and magnitude of inflammatory markers was similar to the placebo treatment. Based on the results of the study, it does not appear that CBD is an effective supplement in mitigating performance loss or attenuating muscle damage and inflammation following intense eccentric exercise in female collegiate athletes. For individuals who exercise and athletes attempting to minimize fatigue associated with intense exercise, CBD supplementation does not appear to be an effective treatment.

Participant Characteristics

Female collegiate athletes were targeted for this study in an attempt to control for any acute training effects that may have occurred throughout the performance testing protocol, as well as differences in physiological response seen following exercise, in an untrained population. In total, 24 participants completed all data collection requirements for the study. More specifically, female NCAA division I (n = 7) and division II (n = 17) athletes in the sports of volleyball (n = 2), basketball (n = 2), soccer (n = 8), gymnastics (n = 6), stunt (n = 1), and softball (n = 5) completed all procedures.

Cannabidiol Supplementation and Exercise

CBD supplements can be classified as either full spectrum or isolate. CBD isolate contains only CBD, with all other phytochemicals removed. Full spectrum supplements contain

CBD, as well as all other compounds naturally occurring in the Cannabis plant. This difference should be noted, as full spectrum CBD may elicit a different physiological response (Russo, 2019). For the purposes of the current study, CBD isolate was chosen as the treatment due to the regulations within the NCAA and Texas state law, as well as the lack of research that includes supplements containing on the phytocannabinoid CBD.

Until recently, no published evidence on the effectiveness of CBD supplementation existed following exercise in human participants. With the increase in popularity of CBD supplementation and exercise, research on this topic is becoming more prevalent. Recently, 60 mg of CBD following exercise was found to attenuate creatine kinase and Mb response after 72 hrs (Isenmann et al., 2021). A back squat and depth jump protocol was utilized to elicit muscle damage in 16 participants. One 60 mg dose of CBD or placebo was given orally following exercise, though it is unclear whether the CBD that was administered was isolate or full spectrum. After 24 and 48 hrs no difference in creatine kinase and Mb levels were observed, which compliments the results of the current study. Baseline Mb values for this study are not available, but following muscle damage participants serum Mb levels climbed to 31.5 ng/mL which is similar to the 32.77 ng/mL seen in the current research. An interesting finding from this study, according to Isenman et al. (2021), blood was analyzed at 72 hrs post muscle damage and a statistically significant difference in creatine kinase and Mb concentrations between those who consumed CBD and placebo was observed. An extended timeline may be needed to see a benefit with CBD supplementation with regard to markers of muscle damage.

In another recent study, CBD oil was not able to reduce perceived soreness in untrained participants 24 and 48 hrs following a muscle damaging session (Cochrane-Snyman et al., 2021). However, the composition of the CBD treatment (isolate vs. full spectrum) was unclear, thus it is

difficult to relate to the current research. Similar to the current study, no significant differences were observed with VAFS scores between those that consumed CBD and a placebo at any time (Cochrane-Snyman et al., 2021). No significant benefit of CBD supplementation with regards to restoring performance loss following muscle damage has been documented (Cochrane-Snyman et al., 2021; Isenmann et al., 2021), thus complementing the results of the current study.

Currently, it is unclear what physiological mechanism would be responsible for changes in muscle damage, performance, or inflammation that could prove beneficial following strenuous exercise. It is hypothesized that the anti-inflammatory effects of CBD occur primarily through the nuclear factor-κB (NF-κB) pathway. NF-κB, is a group of transcription factors, play a large role in the body's immune and inflammatory response (Liu et al., 2017). Dysregulation of NF-κB signaling is associated with a number of conditions, including rheumatoid arthritis, inflammatory bowel disease, MS, atherosclerosis, type I diabetes, chronic obstructive pulmonary disease, and asthma (Liu et al., 2017). Following intense exercise NF-κB signaling is associated with the inflammatory response (Gomez-Cabrera et al., 2006). While no research has been conducted with human participants, CBD was able to reduce NF-κB signaling and decrease levels of inflammatory cytokines (TNF-α, IL-6, and IL-1β), while increasing anti-inflammatory (IL-10) cytokine production, in both *in vitro* and *in vivo* studies (Kozela et al., 2010; Mammana et al., 2019).

Inflammatory Response to Exercise

While intense, acute exercise increases the inflammatory response and may be perceived as damaging, the body's ability to adapt to this response through consistent exercise may have an overall, chronic anti-inflammatory effect (Allen et al., 2015). The inflammatory response following an acute bout of exercise is directly dependent on the intensity, duration, and mode of

exercise, as well as the sex, age, and training status of the participant (Peake, Neubauer, Walsh, & Simpson, 2017). This response plays an important role in the adaptive response of skeletal muscle following exercise, and is characterized by a release of several cytokines in an ordered process (Pournot et al., 2011). CBD supplementation was unable to mitigate the inflammatory or increase the anti-inflammatory response with several cytokines (IL-1β, IL-10, IL-6) following 100 eccentric knee extension repetitions in 24 female collegiate athletes.

The systemic inflammatory response following intense exercise begins with an influx of macrophages, neutrophils, and monocytes, stimulating the influx of cytokines (Peake et al., 2005). The pro-inflammatory cytokine IL-1β is produced and released in a variety of cell types, and acts as an important mediator in the inflammatory response (Lopez-Castejon, & Brough, 2011). Following a marathon, IL-1β levels can be increased over 350% and remain elevated for more than 5 days (Passos et al., 2019). Carbohydrate intake, antioxidant supplements, and cryotherapy may suppress IL-1β levels following the onset of stress (Passos et al., 2019; Pournot, 2011; Vassilakopoulos, 2003). In the current study, no significant (p = .573) differences in IL-1β between the CBD and placebo treatments across any of the four observed trials were observed.

IL-6 levels can increase up to 100-fold following exercise, and the magnitude of IL-6 response is directly related to the intensity and duration of exercise, as well as the glycogen content of the muscle (Pedersen, 2000). Released from the working muscle into circulation during exercise, IL-6 is primarily categorized as a pro-inflammatory cytokine, though it can stimulate the release of anti-inflammatory cytokines such as IL-10 and IL-1ra, and suppress concentrations of the pro-inflammatory cytokine TNF-α (Pedersen & Fisher, 2007). Following intense eccentric exercise, a rise in IL-6 is significantly correlated to the subsequent rise in serum

markers of muscle damage (i.e., creatine kinase, Mb, lactate dehydrogenase; Pedersen et al., 2001). With this broad spectrum of mechanisms of action, regulation of IL-6 could play an important role in an individual's ability to achieve a high-performance state following strenuous exercise. Interleukin-6 concentrations following strenuous, eccentric exercise can vary. For example, Willoughby et al. (2003) observed a 3-fold increase following 70 repetitions of eccentric exercise (i.e., back squat; Willoughby et al., 2003). Smith et al. (2000) reported similar results following 48 eccentric repetitions of leg curl and bench press exercises (Smith et al., 2000). However, Wilborn et al. (2017) observed no significant rise in IL-6 levels 24 hrs following 240 eccentric leg extension reps (Wilborn et al., 2017). Similarly, Cornish and Johnson (2014) reported no changes in IL-6 concentrations following 60 repetitions of eccentric leg extension (Cornish & Johnson, 2014). In the current study, serum levels of IL-6 in female collegiate athletes did not significantly differ between those that consumed CBD or a placebo or across multiple timepoints following 100 repetitions of eccentric leg extensions. Additionally, there were no significant differences between trials, indicating the muscle damaging stimulus may not have been demanding enough to elicit an inflammatory response as seen in studies using a similar protocol. These results, in addition to IL-1β concentrations being unchanged, suggest that supplementation with CBD may not have the ability to limit the inflammatory response following exercise.

CBD has been marketed and sold as containing anti-inflammatory ingredients, and is thus helpful when it is consumed following exercise. When given 5 mg/kg of CBD isolate 2 hrs prior to, immediately after, and 10 hrs after intense eccentric exercise, there was no significant (p = .573) increase in the anti-inflammatory cytokine IL-10 when compared to a placebo. IL-10 is a cytokine that interacts with immune and nonimmune cells, and acts to mitigate the inflammatory

response following stress (Cabral-Santos et al., 2019). The primary function of IL-10 is to regulate and ultimately stop the inflammatory response across several cell types, and may also enhance myogenesis (Deng et al., 2012; Rodas et al., 2020). There is no agreement as to the nature of response of IL-10 following intense eccentric exercise. Hirose et al (2004) observed a 2-fold increase in IL-10 following 30 repetitions of eccentric elbow flexion (Hirose et al., 2004). However, Cornish and Johnson (2014) reported undetectable IL-10 levels following 60 eccentric knee extensions. Several factors, including sex, training status, and genetic predisposition, may affect the inflammatory response to exercise, which may help explain the variation in research findings. Given the inability of CBD supplementation to reduce serum markers of the pro-inflammatory cytokines IL-1β and IL-6 or increase serum markers of the anti-inflammatory cytokine IL-10 following intense eccentric exercise, CBD may not reduce inflammation, as purported my numerous marketing strategies for the supplement.

Performance

It is not uncommon for professional, collegiate, and even amateur athletes to be asked to complete incredibly demanding maximal-effort competitive sessions on less than 48 hrs rest. The ability to reduce fatigue and minimize performance loss between these sessions can play a vital role in subsequent performances. Perhaps more importantly, injury rates are higher when athletes are asked to perform competitive efforts on short (24 to 48 hrs) rest (Mason et al., 2021). Moreover, training status is an important factor in an individual's ability to recover from exercise, with lesser trained athletes possessing a slower return to a resting state with regard to inflammation, force production, autonomic nervous system activity, soreness, and performance (Halson, 2014). Participants in the current study were well-trained, with each participant competing at their respective sport for a minimum of 6 years.

Compared to 60º/sec peak torque and 5-sec isometric peak torque, the remaining measured performance variables (i.e., peak torque at 180 and 300 º/sec and vertical jump) require less sustained maximal contraction, and are rather explosive in nature. A significant loss in performance across both treatments at 4 and 24 hrs following muscle damage with regards to 60º/sec peak torque (p = 0.003 and 0.001, respectively) and 5-sec isometric peak torque (p = 0.034 and 0.023, respectively) was observed. This was expected, as it is known that following muscle damage, sustained maximal contractile strength is among the first physiological variables to decline, while high speed sub-maximal contractile properties remain stable (Newham et al., 1991). Central fatigue is a likely contributor to this observation, as the decrease in sustained maximal contractile strength is due to impaired muscle function, and the ability of the central nervous system to optimally activate the muscle (Carroll et al., 2017).

Muscle Damage and Fatigue

Eccentric exercise protocols are commonly used to induce muscle damage in research settings (Proske & Morgan, 2001). The key mechanisms associated with eccentric EIMD are disruption to the sarcomere, dysfunction of the excitation-contraction (E-C) coupling process, and the acute inflammatory response (Proske & Morgan, 2001). These factors result in a decrease in subsequent performance capabilities that can last from hours up to several days, depending on the magnitude of damage and training status (Skorski et al., 2019).

There is significant debate with regard to the identification and quantification of EIMD (Malm, 2001). Several methods of determining the severity of EIMD include the use of blood marker concentrations, MRI, muscle biopsy, subjective soreness scales, and girth measurements (Brancaccio et al., 2010). Of these methods, changes in blood serum muscle proteins is a commonly used and accepted method of determining the scope of EIMD. Serum levels of

creatine kinase, Mb, and lactate dehydrogenase are the most commonly used proteins in identifying EIMD (Driessen-Kletter et al., 1990). For this research study, Mb was chosen due to the short time to peak (i.e., 24 hrs), and faster return to baseline, compared to other muscle proteins (Driessen-Kletter et al., 1990).

Supplementation (i.e., BCAAs, Omega 3s, antioxidants, carbohydrate/protein mixes) that aims to reduce EIMD can yield varying results (Cheshier & Jacobson, 2021; Kerksick et al., 2018; Sousa et al., 2014). CBD supplementation in the current study was given 2 hrs prior to the muscle damaging protocol allowing for ample time to reach max concentrations in the system (Millar et al., 2018). Results found no significant differences ($p = 0.116$) in EIMD, as indicated by Mb levels between those that consumed CBD or a placebo was observed. Peak concentration of CBD can be reached between 1.5 and 3 hrs following oral ingestion indicating that CBD levels were at or near peak concentrations during the muscle damaging session (Millar et al., 2018). The current results indicate CBD was not effective at reducing EIMD following intense eccentric exercise. Therefore, it does not appear that CBD supplementation at an oral dosage of 5 mg/kg is able to attenuate Mb response following intense eccentric exercise.

An individual's prior training history and current training status play a large role in the magnitude and duration of EIMD following strenuous exercise (Tee et al., 2007). The time required for Mb levels to return to baseline is increased for untrained individuals when compared to trained individuals. In this study, a significant ($p = 0.002$) rise in Mb levels 4 hrs after participants performed 100 repetitions of eccentric knee extensions was recorded, with Mb levels returning to near baseline after 24 hrs. In untrained participants, Mb levels remained significantly increased after 48 hrs using a similar protocol (Kanda et al., 2013; Tartibian et al., 2011). The results of the current study are similar to previous studies in which Mb returned to

baseline 24 hrs following intense exercise in trained athletes (Chase et al., 2020; Takarada, 2003).

The magnitude of Mb response is associated with the mode, intensity, and duration of the exercise performed. For example, peak Mb values of 970.3 ng/mL were recorded following a simulated basketball game with trained individuals (Kostopoulos et al., 2004). In another study, Mb concentrations reached a peak of 9,748 ng/mL in elite runners following a 24 hr marathon (Chalchat et al., 2021). These differences in peak values can likely be explained by the duration between the exercise modalities. Resistance training muscle damaging protocols appear to elicit a lower Mb response than modalities that combine both aerobic and resistance training. For example, following an intensive back squat and plyometric protocol in well-trained participants, Mb values were only 37.5 ng/mL 4 hrs following the protocol (Isenmann et al., 2021). In a similar study, peak Mb values of 79 ng/mL in well-trained runners were observed after a muscle damaging protocol using the elbow flexors (Machin et al., 2014).

Subjective measures of fatigue have also been used in research to give investigators an indication of the magnitude of fatigue and EIMD. The VAFS is a valid and reliable method of measuring fatigue (Tseng et al., 2010). In the current study, subjective fatigue at 4, 24, and 48 hrs after muscle damaging session were all significantly (p = 0.00, 0.00, and 0.01, respectively) elevated over baseline. Participants in this study perceived fatigue with both treatments, and were thus less prepared to perform at an optimal level up to 48 hrs following the muscle damaging session. Previous researchers have hypothesized that CBD may allow for a beneficial outcome with VAFS scores due to the anxiolytic effects of CBD (de Souza Crippa et al., 2004). In the current study, CBD was not able to significantly (p = 0.126) reduce VAFS scores, indicating that CBD is not effective in reducing subjective measures of fatigue and EIMD.

Subjective measures of fatigue were measured immediately following collection of performance measures. This order was chosen rather than completing the VAFS prior to performing performance measures in order to allow participants to compare their efforts to trials passed. The specific performance measurement exercises were in-part chosen as they are non-fatiguing in nature and easily replicated without causing prolonged fatigue when utilizing an appropriate rest interval. This fact coupled with the use of female athletes as participants provides rationale for not performing VAFS collection prior to performance measures.

HRV and Muscle Damage

HRV has been well established as an accurate and reliable measure of autonomic nervous system activity, and is commonly used to determine an individual's ability to recover from intense exercise (Flatt et al., 2018). Many factors may influence the day-to-day fluctuations in HRV, including training status, exercise, mental stress, inflammation, and hormone levels (Fatisson et al., 2016). Iizuka et al. reported HRV to be an accurate means of objectively measuring fatigue in well-trained participants, yet the direct relationship between muscle damage, fatigue, and HRV is still largely unknown (Iizuka et al., 2020). A correlation between perceived pain levels and an increase in sympathetic nervous system activity has been established (Hamunen et al., 2012; Schlereth & Birklein, 2008); however, the physiologic basis for this link has not been elucidated. Following intense exercise, damage to the myofibrillar structure and connective tissue, and inflammation can all play a role in the magnitude of delayed onset of muscle soreness (Cheung et al., 2003). While the direct relationship between serum markers of muscle damage and subjective measures of muscle soreness remains unclear, it is known that muscle damage and soreness develop concurrently (Nosaka et al., 2002). It therefore follows that increases in serum levels of markers of muscle damage leads to an increase in

sympathetic nervous system activity, evident through a decrease in HRV. HRV was collected and analyzed in the study to better understand the role of physiological muscle damage. A weak (r = 0.10) positive relationship between serum Mb levels and HRV measures was recorded. This data contradicts previous research collected in our laboratories, in which a significant negative relationship (p = 0.035) was found between HRV and creatine kinase levels. The differences in these results make it is difficult to determine what role, if any, serum markers of muscle damage play in day-to-day changes in HRV, thus further research is warranted.

A *posteriori* power analysis was computed using statistics software (IBM SPSS Statistics v.24, Armonk, NY) in order to help determine if proper sample size was obtained from recorded values. Observed power for each interaction (i.e., treatment, trial, and treatment*trial) was found using means and standard deviations from the data set. Trial and treatment*trial interaction resulted in observed power levels of 0.76, and 0.43, respectively. These values fell below the *a priori* desired power of 0.80 suggesting that more participants may have been needed to reduce the likelihood of a type II error. Findings from the treatment*trial interaction are not uncommon with regard to non-significant findings for RM MANOVA, as power calculations for such statistical analysis are often underpowered (Aguinis, 1995).

Limitations

There were several limitations to this study. The use of only female collegiate athletes may have affected the outcome of the study. Previous research demonstrates that differences exist with regards to the hormonal and inflammatory response to exercise based on age, sex, and training status of the participant, thus the results of this study may only be presumed accurate for well-trained females between the ages of 18 and 26 years (Dannecker et al., 2012).

The specific CBD product and dosage chosen may also be a limitation. CBD was administered in pill form, which has been shown to have a slower absorption rate and lower peak concentration when compared to CBD administered via oils, inhalation, or injection (Millar et al., 2018). Due to these factors, a higher dosage was needed with for oral pill administration. Although carefully selected after a thorough review of the literature, the selected timing dosage (3 doses of 5 mg/kg) of CBD may be a potential limitation.

No significant time interaction between treatments were observed with regard to Mb (p = 0.116), VAFS (p = 0.126), and performance measures (p = 0.443), indicating baseline measurements for both the CBD and placebo treatments were similar. Baseline measurements for inflammatory cytokines revealed significant differences between the CBD and placebo treatments for IL-10 (p = 0.14), and IL-6 (p = 0.10) concentrations. These differences in baseline measures, as well as the large coefficient of variance observed, are not uncommon in research (Ter Horst et al., 2016). Several factors such as genetics, environment, gut microbiome, diet, and immune function can lead to a large variation in cytokine production (Schrimer et al., 2018). The participant demographic chosen for this research aimed to minimize this individual variation through including only female collegiate athletes, but high coefficient of variation with regards to inflammatory markers was still observed.

The inflammatory cytokines IL-1β, IL-10, and IL-6 were analyzed using a Luminex MagPix® system. While this method provides efficiency via multispec analysis (i.e., multiple targets analyzed per well) there are potential errors in detection due to intraplate variance of the magnetic beads. In other cases, samples may be out of the detectable range. Because of these factors, the research team was forced to omit several samples, due to either low detectability in the sample or errors in the analysis of magnetic beads. This is a limitation of the study as it was

not financially feasible to purchase the required supplies to remeasure samples. In addition, while preparing and analyzing the inflammatory markers, several potential obstacles were overcome. Maintenance issues with machinery, and electrical issues within the storage refrigerators may have impacted the sensitivity of the assays.

Future Research

The effects of CBD supplementation with exercise responses are currently an understudied line of research. With regards to performance, muscle damage, and inflammation, it would be worthwhile to repeat the current study using full spectrum CBD. The recruitment of non-NCAA, well-trained athletes should be performed in order to increase the generalizability of the results. A more robust muscle damaging protocol that incorporates an aerobic component, to elicit a larger inflammatory response, should also be included in future studies. A more comprehensive investigation of muscle damage through investigating additional measures (i.e., markers obtained from muscle biopsy, MRI results) could prove beneficial. Given the differences in the response to intense exercise between the sexes, an equal number of male participants matched for age, BMI, and fitness status should be recruited (Dannecker et al., 2012).

Conclusion

The ability to improve performance through enhancing recovery has recently gained in popularity. Modalities such as self-myofascial release, compression garments, massage, and cold-water immersion may expedite the recovery process following exercise (Davis et al., 2021). Nutritional interventions have also shown to be of benefit, including BCAAs, nitrates, and HMB (Kerksick et al., 2018). The purpose of this study was to determine if CBD supplementation reduces fatigue and inflammation, and enhances performance, following eccentric exercise.

CBD was unable to lower subjective fatigue scores, mitigate muscle damage, expedite a return of performance, or limit the inflammatory response in female collegiate athletes. CBD therefore is not recommended as an effective addition to an individual's recovery protocol. It is recommended that further research with varying CBD supplements be conducted in order to determine if other phytochemicals found in the cannabis plant prove effective as a means of expediting recovery.

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APPENDIX A

INFORMED CONSENT, INCLUSION CRITERIA CHECKLIST, FLYER, PAR Q

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TEXAS WOMAN'S UNIVERSITY

TEXAS WOMAN'S UNIVERSITY
CONSENT TO PARTICIPATE IN RESEARCH
for a Research Study entitled

"THE EFFECTS OF CANNABIDIOL ON MARKERS OF PERFORMANCE FOLLOWING ECCENTRIC EXERCISE"

SUMMARY AND KEY INFORMATION ABOUT THE STUDY

You are being asked to participate in a research study at Texas Woman's University. The purpose of this research is to determine if cannabidiol (CBD) supplementation can aid in the recovery from strenuous exercise. You have been invited to participate in this study because you are a young, healthy, female who participates in strenuous exercise on a weekly basis. You will be asked to perform two muscle damaging sessions separated by approximately 30 days. Following the muscle damaging sessions you may experience some muscle soreness, reduced range of motion, and minor swelling of the damaged muscles. Blood will be collected 2 hrs prior to, and 4, 24, and 48 hrs following the muscle damaging protocol. You will also be asked to perform three measures of performance immediately prior to, and 24 and 48 hrs following, the muscle damaging protocol in order to determine the magnitude of performance loss. There will be 7 total visits and the approximate time commitment is 16.5 hours. Following completion of the study, you will receive a $50 Visa gift card. The greatest risks of this study include injury/discomfort/soreness from performing strenuous exercise and bruising or infection from blood collection. We will discuss these risks and the rest of the study procedures in greater detail below.

Your participation in this study is completely voluntary. If you are interested in learning more about this study, please review this consent form carefully and take your time deciding whether or not you want to participate. Please feel free to ask the researchers any questions you have about the study at any time.

INVITATION and PURPOSE

You are being asked to participate in a study that examines the effects of cannabidiol (CBD) supplementation on recovery from strenuous exercise. Cannabidiol has been

shown to have anti-oxidant and anti-inflammatory properties, some of which may be beneficial following exercise. **The purpose of this study is to determine if CBD supplementation can aid in the recovery from strenuous exercise.**

PARTICIPANT REQUIREMENTS and PRELIMINARY SCREENING

Participant Criteria

There will be 24 females recruited for this study. Enrollment is open women of all ethnicities. In order to be eligible to participate, you must have the following characteristics:

1. have participated in an average of 7 hours per week of strenuous exercise
2. are 18-26 years of age
3. are deemed healthy as determined by a PAR Q+ questionnaire
4. have the ability to follow verbal directions

In addition, you may not enroll in the study if you have/had: 1) musculoskeletal injuries within the previous 30 days that has limited the ability to train; 2) any surgeries in the prior 6 months; 3) orthopedic problems that could be exacerbated by exercise; 4) cardiovascular issues that may affect heart rate variability or preclude them from exercise; 5) consumption of any cannabis product or byproduct in the previous 6 months; 6) consumption of any anti-inflammatory medication for the previous 14 days; 7) chronic exposure to, or consumption of, nicotine products within 30 days, 8) consumption of any alcohol within the 48 hours prior to beginning the study, and; 9) are not pregnant or breastfeeding.

EXPERIMENTAL METHODS and APPROACH

You are asked to read and sign this form before entrance into this study and data collection begins. All testing sessions will take place in rooms 114 and 123 in Pioneer Hall, Texas Woman's University, Denton, TX.

A double-blind, placebo-controlled, repeated-measures design will be used to determine if differences exist with regards to markers of muscle damage, inflammation, and performance. You will be asked to complete 7 visits in total, with visit 1 being a familiarization session, visits 2 and 5 consisting of performance measurements followed by the muscle damaging protocol. Visits 3, 4, 6, and 7 will consist of blood collection and performance measures only. With regard to timeline, visits 1-4 will occur over a period of 50 hours. Approximately 30 days later (to coincide with similar phase of menstrual cycle), visits 5-7 will occur over a period of 50 hours. This does not mean the visits together total 50 hours, just that they will take place within a 50-hour time period.

Visit 1 – Familiarization Session

Following recruitment, a familiarization session will be held. You will be asked to complete a PARQ form and this informed consent document at this time. You will be shown all of the equipment used in the study. Researchers will randomize the treatment you will receive first, as well as the leg you will use for each trial using a research

randomizer website (www.randomizer.org). Once randomly assigned to a treatment group, you will notify the researchers upon onset of menses, at which point visit 2 will begin within 7 days. A washout period of approximately 4 weeks will be completed to allow for standardization of the menstrual phase and to ensure complete recovery from the muscle damaging protocol. You will be required to comply with all exclusion criteria in the period between visits 4 and 5.

Visits 2 & 5 – Muscle Damaging Sessions

For muscle damaging sessions, you will be asked to report to the laboratory at 07:00 for each session following an 8 hr fast (water only, no caffeine) and have performed no strenuous physical activity for 72 hrs prior. Weight (kg) using a digital scale (Tanita BWB-800, Arlington Heights, IL) and height (cm) using a stadiometer (visit 2 only; Perspective Enterprises Model PE-AIM-101) will be recorded first. A blood sample will then be collected. Next, you will be asked to orally consume the appropriate treatment, either 5 mg/kg of cannabidiol) or a placebo, and researchers will note the time in order to begin the muscle damaging session 2 hours following consumption of the treatment. You will then be asked to consume a standard snack following blood collection consisting of 4 kcal/kg of body weight (Clif Bar & Company, Emeryville, CA; 250 kcal per 68 g serving; 18% fat, 68% carbohydrate, 14% protein). You will then be free to leave the laboratory and will report back 2 hours following consumption of the treatment, or at approximately 09:30. You will be asked to refrain from ingesting anything other than water or participating in physical activity outside of walking during this period.

Performance Measures

Upon returning to the lab, you will complete a 10-minute warm-up at a self-selected cadence, maintaining heart rate (HR) under 60% of their age-predicted maximum heart rate on an electronically braked cycle ergometer (Ergomedic 828E; Monark Exercise AB, Vansbro, Sweden). After completing the 10-minute warm-up, you will be asked to complete a static vertical jump test utilizing a Just Jump mat (Probotics, Huntsville, AL). You will be allowed 5 sub-maximal warm-up vertical jumps with 30 seconds of rest between jumps prior to beginning the test. You will step on the mat and place your hands on your hips. You will then be instructed to bend until the knees are at 45° of flexion (halfway down) and remain in that position for a minimum of 2 seconds before performing a maximum effort vertical jump. You will be asked to perform 3 maximum effort jumps with 1 minute of rest between each repetition.

All strength testing and the muscle damaging protocol will be carried out using a Biodex System-3 isokinetic dynamometer (Biodex Medical Systems, Inc., NY, USA). To familiarize yourself with the Biodex dynamometer, you will be allowed 5 repetitions at each speed at 50% of perceived maximal effort at each of the three tested speeds. In order to measure dynamic strength of the knee extensors (muscles), you will be asked to complete 10 maximal repetitions at various velocities. The range of motion for the dynamic strength test will start at 0° of knee flexion (straight knee) and end at 90° of knee flexion (bent-knee). One minute of rest will be given between each set, with the researchers recording average peak torque (Nm) and total work (J) for analysis.

After a 3-minute recovery period, you will be asked to complete the isometric strength test on the Biodex dynamometer. Using the knee extensor (muscle) of the leg chosen through random group assignment, you will produce a total of three maximal voluntary contractions for 5 seconds each, with one minute of rest between each repetition. For isometric strength testing, the knee will be at 90° of knee flexion. Peak torque (Nm) will be recorded for each trial. You will complete a 5-minute rest period before beginning the muscle damaging protocol.

Following the performance measures, you will be asked to complete the Visual Analogue Fatigue Scale (VAFS). The VAFS is a vertical 10-cm line with the bottom of the line representing “no fatigue”, while the top of the line represents “very severe fatigue.” You will be asked to draw a horizontal line across the vertical line indicating the level of fatigue you feel between “no fatigue” and “very severe fatigue.” Researchers will measure the vertical distance between the bottom of the scale and the line drawn in millimeters and record that number as the score.

Muscle Damaging Protocol

The muscle damaging exercise protocol will consist of 10 sets of 10 repetitions of leg extensions. This protocol is safe and has been proven to elicit a sufficient muscle damaging and inflammatory response (Willoughby, McFarlin, & Bois, 2003). Participants will complete each set with no more than 3 seconds of rest between repetitions, and 1 minute of complete rest will be given following each set. After completing the muscle damaging protocol, participants will be free to leave the laboratory for 3.5 hours and resume their normal daily nutritional habits. Researchers will record the nutritional intake between leaving the laboratory and returning to the laboratory 4 hours post muscle damaging session. Participants will be instructed to consume the identical nutritional intake for both treatments.

Blood Collection

Blood samples will be drawn at 2.5 hours prior to, and 4, 24 and 48 hours following muscle damaging protocol for each treatment. Each blood sample, excluding the 4-hour post muscle damaging sample, will be performed following an 8-hour fast (water only, no caffeine). For each blood sample, 10 mL of blood will be collected via venipuncture from the antecubital vein, near the elbow. Researchers will alternate arms for each successive blood draw.

Supplementation

Upon completion of the initial (-2 hours) blood collection, researchers will supply you with 5 mg/kg of bodyweight of cannabidiol (IntrinsicHemp, Pewaukee, WI) or a matched weight of placebo (microcrystalline cellulose powder), The same treatment will be given to you immediately following completion of the muscle damaging protocol. You will be provided same treatment as you received for the previous treatment time and instructed to consume the supplement 10 hrs following the muscle damaging protocol. For each treatment, you will be asked to maintain regular nutritional habits until completion of the 48 hrs follow up visit.

Both the placebo and CBD supplementation preparation will be handled by the primary researcher. Treatments will be weighed, measured, labeled and stored in a plastic bag by the primary researcher. In order to blind the primary researcher, a secondary researcher will take each treatment out of the bag and place them in an opaque plastic container with a lid. The containers will then be labeled as “treatment #1” or “treatment #2”, and a secondary researcher will record each participants’ treatment order until the time of data analysis. Secondary researchers will distribute and monitor the pre and immediately post muscle damage treatment consumption with the primary researcher in another room.

Visits 3, 4, 6, & 7 – Performance Measure Sessions

You be asked will return to the laboratory 24 and 48 hours following each muscle damaging protocol and following an 8-hour fast (water only, no caffeine). Blood will be collected upon arrival, and you will be supplied with a Clif bar, similar to visits 1 and 4. You will then begin the same 10-minute warm-up as the muscle damaging session. After completing the warm-up, you will then be measured on static vertical jump, dynamic strength, and isometric strength as outlined in the muscle damaging sessions. Following the performance measures, you will be asked record your fatigue level using the VAFS. Approximately 30 days will separate visit 4 with visit 5, with visit 5 taking place within the early follicular phase (days 2-7 after the start of menses).

Heart Rate Variability

Heart rate variability (HRV) will be recorded with the use of a Polar H7 heart rate monitor (Polar OY, Finland) worn on the chest with a strap. You will be asked to collect HRV upon waking prior to each visit to the laboratory for data collection. Researchers will use the CardioMood (CardioMood, Russia) smartphone application to collect and analyze HRV data. Each HRV recording will be 2 minutes in length, during which time participants will be instructed to maintain a respiration rate of 12-18 breaths per minute using the metronome function of the application. For each recording, researchers will record the root mean square of successive RR interval differences (RMSSD). Researchers will educate you on how to use the app prior to the first data collection day.

RISK	STEPS TO MINIMIZE RISK
Risks associated with submaximal exercise	Risks include injury to muscles, joints, or organs, a sudden cardiac event or even death. You may rest as needed, are encouraged to be properly hydrated, and will undergo proper warm-up and cool-down sessions each testing and training day to minimize the risk of injury. All of the physiologic risks inherent with exercise testing and training will be minimized through preliminary screening, adherence to standards of practice for exercise testing published by the American College of Sports Medicine, and personal monitoring of each test by trained personnel.
RISK	STEPS TO MINIMIZE RISK
Cardiac or cerebrovascular event during high-intensity exercise	The overall risk of a cardiac or cerebrovascular event has been estimated at 6 in 10,000 during high-intensity, maximal exercise tests among healthy individuals and individuals with a known cardiovascular disease (Gibbons et al., 1980). All technicians present during testing and training are certified in CPR and AED techniques.
RISK	STEPS TO MINIMIZE RISK
Shortness of breath, lightheadedness, nausea	High-intensity exercise training has been associated with shortness of breath, light-headedness, and in some cases, nausea. To minimize these effects, proper warm-up, cool-down, and rest periods will be integrated into the visits. You will have close access to water and restrooms if needed. Exercise will immediately cease and you will be placed in a resting (sitting) position in the event of lightheadedness. An active recovery, which is associated with a reduction in these risks, will be implemented. Proper supervision by trained personnel will take place. You will be reminded that you can withdraw from the study at any time.
RISK	STEPS TO MINIMIZE RISK
Injury during the performance and/or muscle damaging sessions	Injuries can occur during the visits, which can include (but are not limited to) falling, collisions with equipment, and injury to soft tissues (muscle, ligaments, tendon, cartilage). To minimize this risk, the protocols will be reviewed with you each day, and you will be familiarized with the proper form of the exercises during the initial familiarization session. If needed, first aid and CPR will be administered immediately.
RISK	STEPS TO MINIMIZE RISK

Loss of confidentiality	It is possible that there might be a loss of participant confidentiality with data stored offline. To minimize this risk, all data forms collected will be coded using alphanumeric IDs. A single identification form linking names with their respective IDs will be kept in a separate folder form the other data. Persons not associated with the study will have no access to the folders. There is also a potential risk of loss of confidentiality in all email, downloading, and internet transactions. Confidentiality will be protected to the extent that is allowed by law.
RISK	STEPS TO MINIMIZE RISK
Coercion	Participation in this research is entirely voluntary. Your decision whether or not to participate will not jeopardize future relations with Texas Woman's University and the School of Health Promotion and Kinesiology. You may withdraw your consent and discontinue participation at any time and for any reason without prejudice. Discontinuing participation will involve no penalty.
RISK	STEPS TO MINIMIZE RISK
Embarrassment	Words of encouragement and motivational language will be spoken by the investigators in the event you are embarrassed due to your performance during the visits. The investigators will remind you that participation is voluntary and that you may withdraw at any time without penalty.
Emotional discomfort	You will be reminded that participation is voluntary and that you may withdraw from the study at any time. You may experience some emotional discomfort based on your physical performance in the visits. Researchers will use positive feedback during each visit to reinforce a positive atmosphere.
Muscle soreness and fatigue	You may feel periods of soreness and/or fatigue during and after the testing and/or muscle damaging sessions. You may take breaks as needed, and proper hydration will be encouraged. Proper warm-up and cool-down sessions will also be integrated into all visits. Researchers will also allow for time during the familiarization visit to ensure that you are comfortable with the biodex apparatus.
Peripheral venous blood draw infection, bleeding, and/or bruising	There is a small risk of the needle going through the vein or not going into a blood vessel. Also, the you may experience discomfort, bleeding, and/or bruising. On a rare occasion, you may feel dizzy or faint. The likelihood of these complications is very remote (about 1 in 10,000), when the procedure is carried out by trained personnel and proper equipment is used. Precautions will be used during all blood draw procedures. Sites for blood draws will be cleaned with alcohol immediately before each blood draw. Each new needle that is opened will be disposed of in proper containers after use. A trained individual (the PI) will obtain these blood samples to minimize these risks. The amount of blood taken over the course of the study is about 80 mL

	and will not affect normal daily activities. A typical donation of blood is about one pint (1 pint = 450mL, American Red Cross).
Risk of ingesting CBD	CBD is a largely untested product. So there may be potential side effects or medication interactions that are unknown, although none have been reported thus far.
Risk of food allergies	Snacks will be provided to participants so there is a risk of a potential food allergy. Researchers will ask participants if they are allergic to any foods prior to giving the participant the snack. Researchers will also read through the list of ingredients on the snack to ensure that each participant is aware of the contents of the snack.
Potential legal conflicts with state / federal laws regarding CBD	The supplement participants will be receiving is derived from hemp which is legal in the state of TX. There is potential that this could change throughout the duration of the study. Researchers will frequently check state policies regarding hemp products to ensure that all state and federal laws regarding hemp derived CBD are followed.
Coronavirus (COVID-19) exposure	The following steps will be taken to minimize the risk of exposure to COVID-19 based on CDC, state, local, and institutional guidelines; A) Prior to conducting research on any participants, researchers will perform a self-screen for the following new or worsening signs and symptoms: cough, shortness of breath, difficulty breathing, chills, repeated shaking with chills, muscle pain, headache, sore throat, loss of taste or smell, diarrhea, or fever. B) Prior to entry to Pioneer Hall for data collection all participants will have temperature checked using a non-contact thermometer. Participants with a temperature of greater than 100 degrees Fahrenheit will be excluded from participating in research for 14-days. C) While collecting data all researchers will wear gloves, lab coats, and protective facemasks. D) All testing equipment will be sanitized using disinfectant spray and wipes before and after each individual use. E) Researchers and participants will maintain a minimum of 6 feet distance if possible. In situations where this is not possible both the researcher and participant will wear a facial covering.

Biochemical Analysis

Concentrations of IL-6, IL-10, and IL-1β will be analyzed with the Luminex MagPix® using a custom bead panel kit (EMD Millipore Corporation, Bellerica, MA, USA). The

analysis will follow the manufacturer's instructions for preparation. This procedure will require 25 ml of each sample in duplicate for each well. In order to analyze creatine kinase (CK) levels, blood will be collected in a serum separator tube, and delivered to Quest Labs within 12 hours for analysis. Researchers will follow the manufacturer's instructions for all procedures, and all measures will be performed in duplicate. Inter-assay and intra-assay coefficients of variation (standard deviation / mean) will be reported.

To complete all requirements of this study, the total time commitment is:

Visit 1:	**30 minutes**
Visit 2:	**6.5 hours**
Visit 3:	**45 minutes**
Visit 4:	**45 minutes**
Visit 5:	**6.5 hours**
Visit 6:	**45 minutes**
Visit 7:	**45 minutes**
TOTAL TIME COMMITMENT:	**16.5 hours**

Participant Benefits

For your participation, you will receive:
1. A $50 prepaid Visa gift card
2. Your individual results from all performance testing and blood measures.
3. A written summary of the findings upon completion of the study.

Potential Risks and Protection of Participants

The researchers will try to prevent any problem that could happen because of this research. You should let the researchers know at once if there is a problem and they will help you. However, TWU does not provide medical services or financial assistance for injuries that might happen because you are taking part in this research.

The researchers will remove all of your personal or identifiable private information from your data and biospecimens. After such removal, the data and biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent.

If you would like to participate in the current study, but not allow your de-identified data to be used for future research, please initial here _____.

YOUR RIGHTS TO PRIVACY

Confidentiality will be protected to the extent that is allowed by law. All individual information obtained in this study will remain confidential and your right to privacy will be

maintained. Data collected will be used for research purposes only and will be limited to access by the investigators of this study. Only data reported as group means or responses will be presented in scientific meetings and published in scientific journals. Data will be destroyed within 5 years of study completion.

QUESTIONS ABOUT THIS RESEARCH

As investigators, it is our obligation to explain all of the procedures to you. We want to make sure that you understand what is required of you and what you can expect from us in order to complete this study. Please do not hesitate to inquire about the research, your rights and responsibilities as the participant, or our roles as the investigators now or at any time throughout the study.

YOUR CONSENT TO PARTICIPATE

Failure to comply with all of the procedures and to follow the instructions necessary for reliable and valid scientific measurements may result in termination of your participation in this study without your consent. You may be asked to withdraw if you fail to comply with all of the requirements for participation listed above. If you are withdrawn from participation by one of the investigators, our decision will not jeopardize your future relations with Texas Woman's University and the School of Health Promotion and Kinesiology.

CONTACT INFORMATION

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YOU WILL BE GIVEN A COPY OF THIS SIGNED AND DATED CONSENT FORM TO KEEP. IF YOU HAVE ANY QUESTIONS ABOUT THE RESEARCH STUDY YOU SHOULD ASK THE RESEARCHERS. IF YOU HAVE ANY QUESTIONS ABOUT YOUR RIGHTS AS A PARTICIPANT IN THIS RESEARCH OR THE WAY THIS STUDY HAS BEEN CONDUCTED, YOU MAY CONTACT THE TEXAS WOMAN'S UNVERSITY OFFICE OF RESEARCH AND SPONSORED PROGRAMS AT 940-898-3378 OR VIA EMAIL AT IRB@twu.edu

Participant's Signature	Date	Investigator Obtaining Consent
Date		
Printed Name		Printed Name

Exclusion Criteria

Please check the box if you meet any of the criteria listed below. If you are uncertain of your response please as the researcher to explain the criteria.

- ☐ Musculoskeletal injuries within the previous 30 days that has limited the ability to train
- ☐ Any surgeries in the prior 6 months
- ☐ Orthopedic problems that could be exacerbated by exercise
- ☐ Cardiovascular issues that may affect heart rate variability or preclude them from exercise
- ☐ Consumption of any cannabis product or byproduct in the previous 6 months
- ☐ Consumption of any anti-inflammatory medication for the previous 14 days
- ☐ Chronic exposure to, or consumption of, nicotine products within 30 days
- ☐ Consumption of any alcohol within the 48 hrs prior to beginning the study
- ☐ Are pregnant or are breast feeding

Participant's Signature	Date	Investigator Obtaining Consent
Printed Name	Date	Printed Name

RESEARCH STUDY

THE EFFECTS OF CANNABIDIOL ON MARKERS OF PERFORMANCE FOLLOWING ECCENTRIC EXERCISE

Be part of an important study that will help us measure the physiological changes that occur with soreness following the ingestion of a novel recovery supplement.

If you are selected to participate you will be required to:
1. Complete 7 laboratory visits in Denton over a period of 1 month
2. Perform strenuous exercise on 2 laboratory visits separated by at least 30 days
3. Submit 2 blood samples on 2 visits, and 1 blood sample on 4 visits for a total of 8 blood samples.
4. Consume cannabidiol, in pill form, on 3 occasions over a period of 12 hrs

Participation is voluntary. All volunteers will receive:
1. A $50 Visa gift card at the conclusion of the study
2. A report of their individual results and a final report of our study results

You may be eligible to participate if you:
1. Female and are not pregnant
2. 18-26 years old
3. Have participated in an average of 7 hrs per week of strenuous exercise for the previous 12 months
4. Are without a diagnosed cardiovascular, pulmonary or metabolic condition
5. Have not been diagnosed with a musculoskeletal condition that would preclude you from exercising safely

For more information please contact:

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Note: There is a potential risk of loss of confidentiality with any email, downloading, and internet transactions

The study is being conducted by the
Exercise Physiology Laboratory
Pioneer Hall room 116
School of Health Promotion and Kinesiology
Texas Woman's University

2018 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it ***does not limit your current ability*** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

☑ **If you answered NO to all of the questions above, you are cleared for physical activity.**
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION
If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness centre may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

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FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you currently have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? *This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm*

If the above condition(s) is/are present, answer questions 3a-3d If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have High Blood Pressure?

If the above condition(s) is/are present, answer questions 4a-4b If **NO** ☐ go to question 5

4a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
4b.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐

5. Do you have any Metabolic Conditions? *This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes*

If the above condition(s) is/are present, answer questions 5a-5e If **NO** ☐ go to question 6

5a.	Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies?	YES ☐ NO ☐
5b.	Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.	YES ☐ NO ☐
5c.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet?	YES ☐ NO ☐
5d.	Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)?	YES ☐ NO ☐
5e.	Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future?	YES ☐ NO ☐

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6. **Do you have any Mental Health Problems or Learning Difficulties?** *This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome*

If the above condition(s) is/are present, answer questions 6a-6b If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
6b.	Do you have Down Syndrome **AND** back problems affecting nerves or muscles?	YES ☐ NO ☐

7. **Do you have a Respiratory Disease?** *This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure*

If the above condition(s) is/are present, answer questions 7a-7d If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
7b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	YES ☐ NO ☐
7c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	YES ☐ NO ☐
7d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	YES ☐ NO ☐

8. **Do you have a Spinal Cord Injury?** *This includes Tetraplegia and Paraplegia*

If the above condition(s) is/are present, answer questions 8a-8c If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
8b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	YES ☐ NO ☐
8c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	YES ☐ NO ☐

9. **Have you had a Stroke?** *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event*

If the above condition(s) is/are present, answer questions 9a-9c If **NO** ☐ go to question 10

9a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
9b.	Do you have any impairment in walking or mobility?	YES ☐ NO ☐
9c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	YES ☐ NO ☐

10. **Do you have any other medical condition not listed above or do you have two or more medical conditions?**

If you have other medical conditions, answer questions 10a-10c If **NO** ☐ read the Page 4 recommendations

10a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	YES ☐ NO ☐
10b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	YES ☐ NO ☐
10c.	Do you currently live with two or more medical conditions?	YES ☐ NO ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

_____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

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If you answered NO to all of the FOLLOW-UP questions (pgs. 2-3) about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact
www.eparmedx.com
Email: eparmedx@gmail.com

Citation for PAR-Q+
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The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

Key References

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2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance; Consensus Document. APNM 36(S1):S266-s298, 2011.
3. Chisholm DM, Collis ML, Kulak LL, Davenport W, and Gruber N. Physical activity readiness. British Columbia Medical Journal. 1975;17:375-378.
4. Thomas S, Reading J, and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Canadian Journal of Sport Science 1992;17:4 338-345.

01-11-2017

APPENDIX B

CBD SUPPLEMENT LAB ANALYSIS

Report: COA Evaluation Summary

PREE LABORATORIES

OLCC License No. 10087092BDA | ORELAP ID. 4147
545 SW 2nd Street, Corvallis OR. 97333 | 541.257.5002 | services@preelab.com | Preelab.com

For OLCC/OHA Compliance Purposes.

Product Description

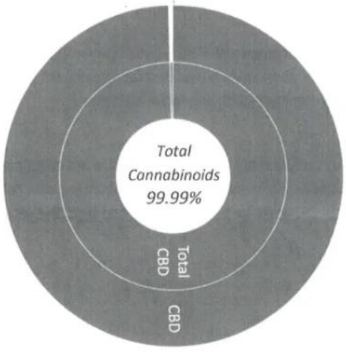
Client:	**GVB Oregon**
Product Name:	**3.24.21 CBD-ISO Batch #8361 Prim**
Matrix:	Hemp Concentrate
Metrc Source ID:	n/a
Metrc Package ID:	n/a
License Number:	n/a
Date Collected:	2021-03-24
Date Received:	2021-03-24
Report Date:	2021-03-27
Report ID:	A3333-01
Tests Requested:	Cannabinoid Potency Analysis Pesticide Analysis Residual Solvent Analysis

Evaluation Summary

Moisture Analysis	Test Not Required

Total THC *
< LOQ
< LOQ

Total CBD *
> 99.99 %
> 999.99 mg/g



Cannabinoid Potency Analysis	Abrv.	Dry Wt. %	Dry Wt. mg/g
	THCA	< LOQ	< LOQ
	Δ-9-THC	< LOQ	< LOQ
	Δ-8-THC	< LOQ	< LOQ
	THCV	< LOQ	< LOQ
	CBDA	< LOQ	< LOQ
	CBD	101.49 %	1014.9 mg/g
	CBGA	< LOQ	< LOQ
	CBG	< LOQ	< LOQ
	CBDVA	< LOQ	< LOQ
	CBDV	0.40 %	4.0 mg/g
	CBN	< LOQ	< LOQ
	CBL	< LOQ	< LOQ
	CBC	< LOQ	< LOQ

Pesticide Analysis	Pesticide Status
Pass	No Pesticides Were Detected above Oregon's action limit as stated in OAR 333-007-0400.

* moisture compensated & adjusted for the loss of carboxylic acid group - OAR 333-064-0100

APPENDIX C
DATA COLLECTION SHEET

Data Collection Sheet

Participant ID		**Trial**	**Limb**

Height (cm)		**Weight (kg)**	
HRV (rmssd)		**VAFS (mm)**	

Vertical Jump		
1	**2**	**3**

Biodex Setup

Seat Fore / Aft		**Seat Height**	
Seat Lateral		**Limb Weight**	

Dynamic Strength Measures

Peak Torque		**60º / sec**	**Avg Power**	
Peak Torque		**180º / sec**	**Avg Power**	
Peak Torque		**300º / sec**	**Avg Power**	

Isometric Peak Torque		
Trial 1	**Trial 2**	**Trial 3**

APPENDIX D

RAW DATA

Descriptive Measures – VAFS – HRV

ID #	Treatment	Trial	Age (yrs)	Height (cm)	Weight (kg)	Covid	Limb	DOM	VAFS (MM)	HRV (RMSSD)
1	CBD	1	22	177.8	80.73	Y	R	Y	86.42	71.77
	CBD	2					R	Y	69.53	
	CBD	3					R	Y	62.4	153.46
	CBD	4					R	Y	49.73	83.32
	PLACEBO	1					L	N	32.33	103.02
	PLACEBO	2					L	N	42.76	
	PLACEBO	3					L	N	49.59	109.72
	PLACEBO	4					L	N	23.67	106.87
2	CBD	1	21	176.4	82.55	Y	R	Y	34.93	72.76
	CBD	2					R	Y	70.2	
	CBD	3					R	Y	51.8	71.95
	CBD	4					R	Y	27.3	118.62
	PLACEBO	1					L	N	47.35	75.42
	PLACEBO	2					L	N	61.5	
	PLACEBO	3					L	N	63.5	42.98
	PLACEBO	4					L	N	43.6	93.62
3	PLACEBO	1	21	174	74.82	Y	L	N	64.8	67.54
	PLACEBO	2					L	N	94.9	
	PLACEBO	3					L	N	47.4	129.2
	PLACEBO	4					L	N	32.3	115.3
	CBD	1					R	Y	79.6	134.16
	CBD	2					R	Y	90.3	
	CBD	3					R	Y	81.3	100.18
	CBD	4					R	Y	39	135.55
4	CBD	1	21	170.2	68.04	Y	L	N	15.7	92.48
	CBD	2					L	N	73.5	
	CBD	3					L	N	46.7	48.45
	CBD	4					L	N	26.2	71.7
	PLACEBO	1					R	Y	11	92.48

	PLACEBO	2					R	Y	31.3	
	PLACEBO	3					R	Y	35.1	64.27
	PLACEBO	4					R	Y	50.8	58.52
5	PLACEBO	1	19	167.6	70.3	Y	L	N	21.7	17.45
	PLACEBO	2					L	N	78.4	
	PLACEBO	3					L	N	37.1	73
	PLACEBO	4					L	N	38.8	21.22
	CBD	1					R	Y	0.85	223.5
	CBD	2					R	Y	16.28	
	CBD	3					R	Y	63.2	92.33
	CBD	4					R	Y	22.6	24.16
6	PLACEBO	1	20	175.3	63.54	Y	L	N	43.5	70.53
	PLACEBO	2					L	N	69.8	
	PLACEBO	3					L	N	80.4	34.9
	PLACEBO	4					L	N	51.4	25.36
	CBD	1					R	Y	29.3	25.01
	CBD	2					R	Y	45	
	CBD	3					R	Y	48.23	47.47
	CBD	4					R	Y	29.6	41.86
7	PLACEBO	1	20	154.9	59.95	N	R	Y	29.6	105.32
	PLACEBO	2					R	Y	50.3	
	PLACEBO	3					R	Y	89.2	94.65
	PLACEBO	4					R	Y	82.1	83.14
	CBD	1					L	N	5.5	82.89
	CBD	2					L	N	45.5	
	CBD	3					L	N	44.7	99.29
	CBD	4					L	N	49.6	82.39
8	PLACEBO	1	21	167.6	69.6	N	R	Y	38.77	129.94
	PLACEBO	2					R	Y	67.3	
	PLACEBO	3					R	Y	72.2	46.3
	PLACEBO	4					R	Y	59.5	63.81
	CBD	1					L	N	9.7	129.94
	CBD	2					L	N	16.9	
	CBD	3					L	N	26.1	46.3
	CBD	4					L	N	30.4	63.81
10	PLACEBO	1	21	163.1	59.83	N	R	Y	15.9	90.26
	PLACEBO	2					R	Y	79.9	

	PLACEBO	3					R	Y	89.9	86.83
	PLACEBO	4					R	Y	75.6	69.92
	CBD	1					L	N	1.8	87.37
	CBD	2					L	N	59.8	
	CBD	3					L	N	39.4	76.76
	CBD	4					L	N	37.7	81.32
11	CBD	1	20	153.6	59.9	N	L	N	33.3	117.33
	CBD	2					L	N	91.8	
	CBD	3					L	N	80.1	109.57
	CBD	4					L	N	81.1	122.26
	PLACEBO	1					R	Y	67.2	
	PLACEBO	2					R	Y	87.3	142.23
	PLACEBO	3					R	Y	62.2	162.73
	PLACEBO	4					R	Y	89.6	
12	CBD	1	21	161.3	61.4	N	L	N	17.9	78.53
	CBD	2					L	N	81.9	
	CBD	3					L	N	41.5	74.63
	CBD	4					L	N	67.5	65.61
	PLACEBO	1					R	Y	22.9	68.2
	PLACEBO	2					R	Y	67.1	
	PLACEBO	3					R	Y	43	42.5
	PLACEBO	4					R	Y	59.9	61.7
13	PLACEBO	1	21	175.3	62.23	N	L	N	9.2	93.59
	PLACEBO	2					L	N	41.3	
	PLACEBO	3					L	N	70.3	96.68
	PLACEBO	4					L	N	20.2	107.46
	CBD	1					R	Y	5.5	113.19
	CBD	2					R	Y	14.7	
	CBD	3					R	Y	16.2	108.95
	CBD	4					R	Y	5.6	110.54
14	CBD	1	19	160.1	60.32	N	L	N	31.8	97.09
	CBD	2					L	N	66.5	
	CBD	3					L	N	88.3	85.19
	CBD	4					L	N	59.2	81.71
	PLACEBO	1					R	Y	2.7	108.92
	PLACEBO	2					R	Y	35.6	
	PLACEBO	3					R	Y	55.9	72.92

	PLACEBO	4					R	Y	33.5	72.51
15	PLACEBO	1	22	165.1	67.13	N	R	Y	41	107.3
	PLACEBO	2					R	Y	62.6	
	PLACEBO	3					R	Y	64.2	37.1
	PLACEBO	4					R	Y	50.7	144.8
	CBD	1					L	N	51.5	14.2
	CBD	2					L	N	92.9	
	CBD	3					L	N	74.6	127.1
	CBD	4					L	N	90.6	
17	CBD	1	18	152.4	50.7	N	L	N	11.67	38.22
	CBD	2					L	N	53.5	
	CBD	3					L	N	64.1	
	CBD	4					L	N	28.2	23.88
	PLACEBO	1					R	Y	75.12	16.05
	PLACEBO	2					R	Y	13	
	PLACEBO	3					R	Y	26.2	28.45
	PLACEBO	4					R	Y	1.2	34.2
18	PLACEBO	1	21	160.2	45.8	Y	L	N	8.2	12.42
	PLACEBO	2					L	N	9.4	
	PLACEBO	3					L	N	17.3	5.63
	PLACEBO	4					L	N	21.2	209.29
	CBD	1					R	Y	3.4	266.81
	CBD	2					R	Y	15.6	
	CBD	3					R	Y	26	
	CBD	4					R	Y	11.9	89.94
19	PLACEBO	1	25	166.4	71.81	Y	L	Y	21.2	64.3
	PLACEBO	2					L	Y	38.9	
	PLACEBO	3					L	Y	50.8	55.1
	PLACEBO	4					L	Y	34.3	68.2
	CBD	1					R	N	6.9	74.1
	CBD	2					R	N	38.9	
	CBD	3					R	N	39.8	64.2
	CBD	4					R	N	24.6	73.1
20	CBD	1	24	167.7	68.43	N	L	N	0.5	108.4
	CBD	2					L	N	21.2	
	CBD	3					L	N	28.4	
	CBD	4					L	N	11.9	

	PLACEBO	1					R	Y	1.1	68.7
	PLACEBO	2					R	Y	18.9	
	PLACEBO	3					R	Y	65.1	
	PLACEBO	4					R	Y	36.6	
22	PLACEBO	1	19	155.9	53.9	Y	L	N	44.6	95.01
	PLACEBO	2					L	N	86.2	
	PLACEBO	3					L	N	84.4	23.5
	PLACEBO	4					L	N	93.2	88.4
	CBD	1					R	Y	35.4	71.2
	CBD	2					R	Y	11.5	
	CBD	3					R	Y	21.8	44.6
	CBD	4					R	Y	32.8	88.2
23	CBD	1	21	172.7	69.39	N	R	Y	43.2	
	CBD	2					R	Y	48.1	
	CBD	3					R	Y	46.3	48.21
	CBD	4					R	Y	47.3	
	PLACEBO	1					L	N	44.8	115.8
	PLACEBO	2					L	N	60.4	
	PLACEBO	3					L	N	65.6	
	PLACEBO	4					L	N	44.2	
24	PLACEBO	1	25	165.6	52.2	N	R	Y	19.7	113.96
	PLACEBO	2					R	Y	21.9	
	PLACEBO	3					R	Y	20.3	204.2
	PLACEBO	4					R	Y	17.1	134.2
	CBD	1					L	N	2.6	85.67
	CBD	2					L	N	7.5	
	CBD	3					L	N	8.9	84.55
	CBD	4					L	N	9.6	71.24
25	CBD	1	24	156.7	64.41	N	R	Y	31.1	71.24
	CBD	2					R	Y	19.7	
	CBD	3					R	Y	32	63.18
	CBD	4					R	Y	21.9	58.02
	PLACEBO	1					L	N	16.7	68.02
	PLACEBO	2					L	N	22.97	
	PLACEBO	3					L	N	28.4	55.21
	PLACEBO	4					L	N	9.5	57.88
26	PLACEBO	1	21	173.7	77.11	N	L	N	6.1	79.26

	PLACEBO	2					L	N	30.1	
	PLACEBO	3					L	N	37	64.48
	PLACEBO	4					L	N	25.3	70.09
	CBD	1					R	Y	23.4	68.83
	CBD	2					R	Y	33.7	
	CBD	3					R	Y	20.6	144.56
	CBD	4					R	Y	12.8	28.16
27	CBD	1	21	154.9	65.31	N	R	Y	8.7	
	CBD	2					R	Y	14.3	
	CBD	3					R	Y	23.6	
	CBD	4					R	Y	23.5	
	PLACEBO	1					L	N	25	
	PLACEBO	2					L	N	32.3	
	PLACEBO	3					L	N	31.2	
	PLACEBO	4					L	N	29.8	

Raw Data

Performance Measures

ID	Treatment	Trial	VJ (CM)	60º/SEC		180º/SEC		300º/SEC		ISOMETRIC PEAK TORQUE		MUSCLE DAMAGE
				PEAK TORQUE (N-M)	AVG POWER (W)	PEAK TORQUE (N-M)	AVG POWER (W)	PEAK TORQUE (N-M)	AVG POWER (W)	PEAK (N-M)	AVG PEAK (N-M)	TOTAL WORK (J)
1	CBD	1	43.69	196.9	119.9	121.6	207.3	104.4	269.9	205.9	203.1	2621.1
	CBD	2	40.89	154.7	105.9	103	197.6	96.3	212.8	166.8	157.7	
	CBD	3	42.93	149.2	98.3	107	186	83.8	214.1	186.3	182.5	
	CBD	4	44.45	163.8	107.5	111.8	202.1	80.2	223.5	210.9	200.5	
	PLACEBO	1	43.94	177.7	122.8	130	245	103.9	295.2	202	200.9	2155.1
	PLACEBO	2	41.66	174.1	121.9	129.7	231.3	111.9	271.8	211.6	202.7	
	PLACEBO	3	42.42	174.8	122.8	131.1	248.6	100.2	282	178.6	177.5	
	PLACEBO	4	43.69	175.9	126.3	128.4	237.2	104.2	278.8	202.3	196.4	
2	CBD	1	42.42	170.1	108.1	118.6	223.6	93.6	266.3	154.6	148.1	1298.7
	CBD	2	40.13	133.1	93.1	110	205.6	85.5	238.2	153.1	142.8	
	CBD	3	40.64	141.9	97.8	111.8	203.3	92.3	259.1	144.5	142.8	
	CBD	4	40.84	118.2	83.8	94.8	169.4	75.9	186.5	136.8	159.5	
	PLACEBO	1	41.91	148.3	103.6	112.5	214.8	87.1	230.3	149.9	162.6	1660.3
	PLACEBO	2	40.64	131.9	93.2	114.6	217.2	90.2	252.1	131.4	129	
	PLACEBO	3	40.39	131.5	100.1	111.5	200.3	82.8	205.9	139.4	127.1	
	PLACEBO	4	40.49	147.4	106.8	117.8	224.2	95.1	235.8	143.6	138.9	
3	PLACEBO	1	40.39	132.4	84.6	77.4	125.7	49.2	109.6	145.9	132.8	1359.5
	PLACEBO	2	39.12	127.8	78.7	85.6	117.7	57.4	100.4	151.1	147.3	
	PLACEBO	3	38.1	123	79.6	81.4	135.9	59.7	110.3	150.2	140.2	

	PLACEBO	4	40.39	144.4	90.1	85.6	132.5	48.8	81.1	172.4	149.4	
	CBD	1	41.91	153.6	97.8	103.3	185.3	78.4	200.7	153.5	147.8	1444.2
	CBD	2	41.4	139.2	100.1	99.8	180	76.7	195.7	168.2	149.7	
	CBD	3	41.4	131.8	90.9	96.8	169.2	78	180.8	154.5	148.2	
	CBD	4	42.42	146.4	102.2	114.5	189.5	89.2	211	165.4	161.2	
4	CBD	1	45.72	127.4	84.8	98.9	167.8	73.7	189.4	148.2	138.6	1611.3
	CBD	2	41.15	120.6	80.6	102.1	170.3	71.4	170	126.9	120.4	
	CBD	3	42.42	124.4	91.1	104.1	182	80.3	205.6	157.3	150.5	
	CBD	4	42.67	120.6	86.3	101.9	187.6	78.3	202.9	144.6	135.8	
	PLACEBO	1	47.75	127.5	93.5	99.2	177.6	80.1	217.2	157.1	147.6	1239.7
	PLACEBO	2	41.66	116	75.9	93	155.9	78.9	187.4	123	119.7	
	PLACEBO	3	44.2	112.1	78	94.1	168.7	71.1	181.6	130.6	129.4	
	PLACEBO	4	42.42	104.4	72	92.4	150.3	71.6	174.5	132.1	124.1	
5	PLACEBO	1	36.07	174.8	113.4	92.7	148.4	72	152.7	189.8	183.3	2092.3
	PLACEBO	2	35.56	137.8	95	101.8	155.9	77.3	201.2	164.1	156.4	
	PLACEBO	3	34.8	161.6	111	115	194.3	85.1	222	169.1	122.8	
	PLACEBO	4	35.05	160.8	113.2	114.1	206.9	88.4	243.3	192.6	173.5	
	CBD	1	36.58	170	105.2	122.6	212.8	97.5	245.5	220.1	212.4	1833.9
	CBD	2	35.31	162.8	107	115.4	199.6	91.1	228.4	189.3	178.1	
	CBD	3	35.56	158.1	89.3	110.3	183.7	89	213.4	177.4	168	
	CBD	4	36.32	154.5	98.6	115.5	183.4	91.3	215.3	181.6	168.3	
6	PLACEBO	1	52.07	152.4	78.6	120.4	145.9	107.6	227.1	159.4	150.8	1728.1
	PLACEBO	2	48.77	138.5	82.6	104	166.9	87.4	216.4	156.3	228.5	
	PLACEBO	3	49.53	138.8	86.7	106.3	183.5	83.9	233.4	155.7	145.6	
	PLACEBO	4	48.77	122.2	79.7	110.9	180.8	89.9	227.8	144.2	134.1	
	CBD	1	52.58	149.7	90.9	123.6	205.8	94.9	227.4	173.9	170.4	1516.6
	CBD	2	51.82	152.3	93	121.2	196.2	87.9	229.8	160.2	147.5	

	CBD	3	50.55	147.6	98.6	127.1	205.2	98.7	259.5	193.9	191.7	
	CBD	4	52.58	139.9	78.9	122.4	174.8	102.7	240.6	213.4	200.3	
7	PLACEBO	1	45.21	128	73.7	76.4	121.6	64	172.9	154.9	150.6	1876.7
	PLACEBO	2	44.7	112.2	80	70.9	131.9	55.2	150.4	122.1	114	
	PLACEBO	3	41.66	96.6	64.3	62.3	117.7	50.3	135.7	94.9	93.3	
	PLACEBO	4	44.45	95.9	64.8	58.7	100.7	47	122.4	101.8	96.5	
	CBD	1	48.77	128.3	86.8	84	153	61.1	162.2	156.1	153.9	1514.9
	CBD	2	48.26	127.9	88.6	81.2	149.7	59.4	163.6	167.3	163.8	
	CBD	3	46.74	114.6	74.7	78	139.4	61	167	139.5	138.3	
	CBD	4	47.24	125.4	83.6	80.7	152	62.3	164.2	170.5	164.8	
8	PLACEBO	1	54.61	171.6	109.2	95	160.2	76	168.2	208.5	203.5	2005.4
	PLACEBO	2	53.09	149.4	84.6	108.4	185.5	81.7	205	180.5	168.4	
	PLACEBO	3	49.28	130.1	77.4	96.6	168.5	73.9	202.9	153.9	143.3	
	PLACEBO	4	51.82	142	86.4	97.7	180	77.9	212.3	163.6	158.3	
	CBD	1	52.07	140.1	82.4	102.4	151.6	70.9	169.5	208.2	199.1	1682.4
	CBD	2	51.31	154.8	93	114.8	185.5	85.3	181.5	200.9	197.5	
	CBD	3	51.82	143.3	89.6	102.9	167.8	76.5	179.5	199.1	191.8	
	CBD	4	52.32	156.6	103.8	100.4	164.9	75.6	183.6	233.4	217.9	
10	PLACEBO	1	55.63	166.7	108.6	115.5	189.8	83.1	212.1	177.8	174.8	2292.6
	PLACEBO	2	54.36	121.7	72.5	100.7	175.2	78.2	195.5	146.2	139.8	
	PLACEBO	3	52.83	112.8	69.2	93.6	146.8	81	173.9	137.5	136.2	
	PLACEBO	4	55.12	144.4	88.9	111.7	186.5	83.9	201	144.4	141.9	
	CBD	1	53.34	125.4	76.4	98.2	174.3	74.2	189.6	143.6	134.7	1687.7
	CBD	2	51.05	111.5	71.5	87.9	160.7	70.2	165	135.5	130.2	
	CBD	3	53.09	103.1	68.1	89.3	154.4	65.2	149.2	120.3	115.1	
	CBD	4	53.85	71.2	47.2	64.8	99	54.1	112.4	97.9	95.2	
11	CBD	1	54.86	127.5	80.3	88.2	152.8	70	171.7	132.1	128.8	1299.4

	CBD	2	51.56	118	60.1	85.3	155.3	69.8	171.5	128.5	120.9	
	CBD	3	51.82	127.1	89.4	83.8	154.1	69	169	126.1	121.7	
	CBD	4	54.36	137.6	99	87.7	160	73.6	189.5	132.6	131.9	
	PLACEBO	1	55.12	126.2	81.9	87.1	160.1	73	171	126.7	117.4	927.3
	PLACEBO	2	53.09	116.3	81	89.3	160.6	71.3	179.4	138.8	132.7	
	PLACEBO	3	52.32	109.8	81.6	83.1	148.3	65.1	162.1	131.3	126	
	PLACEBO	4	54.86	113.6	81.5	94.3	167.4	76.1	198.1	129.1	123.6	
12	CBD	1	46.48	153	95.7	98.8	162.8	74.3	195.8	210.6	205.5	1364
	CBD	2	43.69	149.4	86.5	89	135.4	72.1	148.6	185.4	179.3	
	CBD	3	44.7	154.6	97.4	108.6	180	80.4	192.7	205.8	198.3	
	CBD	4	46.48	154.3	100.3	110.4	179.4	89	208.2	226.9	208.5	
	PLACEBO	1	46.99	130.9	79.7	105.9	172.7	82.5	178.8	174.8	167	1154
	PLACEBO	2	46.48	119.5	67.4	99	150.9	73.4	153.7	161.6	157.8	
	PLACEBO	3	43.43	129.6	71.1	100.9	146	81.5	165.8	188.8	180.5	
	PLACEBO	4	45.97	140.1	81.6	106.7	160.9	82.2	176.6	186.6	177.5	
13	PLACEBO	1	75.44	183.8	120.6	134.8	234.9	105.1	281	181	173.4	1387.9
	PLACEBO	2	71.63	156.7	99.8	121.5	202.7	100.5	249.7	164.6	154.5	
	PLACEBO	3	68.07	182.1	110.2	121.3	183.9	86.3	202.2	151.3	144.8	
	PLACEBO	4	70.1	165	101.8	132	209.3	102.8	266.5	140.6	128.7	
	CBD	1	72.39	157.6	91.6	137.9	210.3	100.5	235.8	143.1	137	1069.9
	CBD	2	69.09	132.3	76.9	114.2	166.9	94	186	156.6	144.9	
	CBD	3	70.1	126.5	76.7	119.5	187.2	98.5	195.8	121	117.8	
	CBD	4	68.58	119.1	76.2	108.5	184.7	93.7	186.1	114.6	112.9	
14	CBD	1	49.78	121.6	70.8	83.3	148.4	68.9	178.2	168.1	155.6	1376.7
	CBD	2	48.51	116.7	75.2	77.1	135.2	60	154.4	157.8	155.6	
	CBD	3	46.99	86.8	60.3	78.8	134.3	61.4	146.1	165.8	162.2	
	CBD	4	48.51	129	85.3	79.8	141.6	67.3	173.2	167.6	154.5	

	PLACEBO	1	49.02	127.2	71.7	91.9	154.2	74.2	176.1	141.9	139.6	1106.3
	PLACEBO	2	48.77	121.6	71.4	89.1	150.4	74.7	182	121.9	121.1	
	PLACEBO	3	45.72	97.3	57.9	72.6	109.8	62.6	132.9	151.4	140.6	
	PLACEBO	4	48.01	111.2	66	73.2	112	59.1	138.2	144.8	142.4	
15	PLACEBO	1	48.51	145.6	76.3	116.7	202.4	92.8	238.3	193.7	176.3	1223.8
	PLACEBO	2	43.18	127.2	79.3	110.7	198.2	92.1	241.7	187.3	179.2	
	PLACEBO	3	42.67	123.9	80.8	117.2	198.9	89	225.2	164.8	154.5	
	PLACEBO	4	48.01	131.8	86.9	117.5	199.9	88.9	219.8	190.2	177	
	CBD	1	45.72	135.2	75.1	107.8	184.9	87.4	232.8	173.1	163.7	1122.7
	CBD	2	43.69	93.5	59.4	104.8	161.7	89.6	214.3	142.8	136.8	
	CBD	3	43.18	102.2	62.7	69.5	96.6	48.4	111	140.8	132.4	
	CBD	4	44.7	128.6	74.5	108.9	174.5	92.3	542.5	150.8	147.9	
17	CBD	1	45.97	126.4	73.8	73.8	104.1	60	134.8	133.9	126.4	823.9
	CBD	2	45.47	101.3	57.7	59.4	95.1	59.7	141.8	125.6	118.7	
	CBD	3	43.18	107.8	69.6	71.3	102.4	62.2	144.3	143.7	135.9	
	CBD	4	44.7	105.7	73.9	92.1	141.5	64.8	159.9	133.1	124.1	
	PLACEBO	1	43.43	102.8	67.4	84.6	146.1	71.3	183.4	133.7	133	957.2
	PLACEBO	2	42.67	91.8	50.3	89.6	133	68	156.1	123.3	119.4	
	PLACEBO	3	43.18	79.4	45.4	69.1	116.3	54.2	123.1	139.4	129	
	PLACEBO	4	43.94	99.2	64.1	75.5	130.8	62.5	147.6	149.2	148	
18	PLACEBO	1	50.8	94.4	45.5	59.9	96	57.9	133.4	119.3	112.3	1022.5
	PLACEBO	2	49.28	91.9	51.5	55.4	93.7	53.3	116.3	118.9	117.3	
	PLACEBO	3	50.04	87.4	59.5	69.4	112.2	51.9	122	111	101.1	
	PLACEBO	4	51.05	100.8	67.1	72.5	122.2	60.4	138	121.9	120.9	
	CBD	1	45.47	98.4	58.7	77.1	123.5	62.2	142.1	130.2	124.9	1003.8
	CBD	2	43.94	82.4	55.7	77	117	58.3	127	120.3	117.4	
	CBD	3	46.48	74.4	44.8	70	107.2	56.2	125.2	119.2	109.7	

	CBD	4	42.67	92.8	55.3	73.6	120.7	63.3	148.1	138.3	129.7	
19	PLACEBO	1	53.09	189.9	82.2	109	165.2	90.3	187.8	228	209.5	1877.4
	PLACEBO	2	47.75	138.8	76.9	98.1	142.8	78.7	169.2	215.9	198.6	
	PLACEBO	3	51.82	116.9	63.2	90.2	144.8	73.5	134.4	176.2	169.6	
	PLACEBO	4	52.83	158.2	78.4	108.6	149.8	84.2	173.9	221.3	199.8	
	CBD	1	49.28	131	70.1	99.1	146.1	80	178.1	204.9	184.1	1793.6
	CBD	2	48.01	97.1	58	85.9	132.2	56.9	130.3	203.5	178.1	
	CBD	3	47.24	82.6	55.1	73.6	117.7	81.5	177.1	176.2	170.9	
	CBD	4	51.05	100.2	69.9	98.4	153.2	80.1	187.9	180	177.4	
20	CBD	1	52.07	127.9	85.1	112.3	199.2	84.7	215.1	185.1	180.3	926
	CBD	2	49.28	106.4	68.8	91.3	150.3	79.8	166.8	179.7	174.1	
	CBD	3	48.77	138.8	89.6	103.6	164.9	94.2	199.5	184.6	174	
	CBD	4	50.29	137.8	90.1	108.3	177.2	85.7	188.4	214.2	199	
	PLACEBO	1	51.05	141.7	95.3	122.9	200.9	102.9	229.1	208.5	194.8	1003.8
	PLACEBO	2	48.77	119.9	72.8	99	157.9	90.6	226.5	168	157.3	
	PLACEBO	3	50.04	131.8	84.3	120.7	201.5	99.3	243	186	175.6	
	PLACEBO	4	51.56	134.8	94.4	127	209.8	104.7	211.3	214.5	199.8	
22	PLACEBO	1	41.66	113.5	74.5	68.3	111.3	47.7	90	153.6	138.7	942.6
	PLACEBO	2	39.62	97.7	67.1	37.1	57.8	40.8	93.7	136.5	132	
	PLACEBO	3	39.12	104.3	68.2	65.6	101.5	42.4	91.5	139.4	126.2	
	PLACEBO	4	41.15	102.2	62.7	69.5	96.6	48.4	111	140.8	132.4	
	CBD	1	40.13	107.3	67.5	81.3	130	68.5	147.7	151.4	96.7	531.6
	CBD	2	38.86	97.4	64.7	74.2	118.9	60.2	132.9	144.9	141.2	
	CBD	3	38.61	110.6	70.4	81.4	131.8	73.8	167.5	138.7	136.9	
	CBD	4	40.89	109.9	71	77.2	123.1	60.5	131.6	148.9	180.4	
23	CBD	1	50.04	151.6	100.1	106.4	188.3	84.9	193	177.1	165.8	1537
	CBD	2	47.75	127.8	72.4	73.7	117.6	54.5	132	158.4	141.8	

	CBD	3	47.5	159.6	102.2	110.7	198.4	82.5	183.9	166.1	157	
	CBD	4	49.02	166.7	101.5	112.1	198.8	95.6	230	167.1	160.6	
	PLACEBO	1	51.56	149.3	102.6	102.5	178	87.8	210.5	173.3	160.2	731
	PLACEBO	2	22.1	140.8	96.4	113.6	187.7	77.5	200.3	153.6	145.7	
	PLACEBO	3	49.02	136.9	92	119.6	202.1	90.5	215.8	163	159.7	
	PLACEBO	4	50.04	140.6	98.5	127.9	216	92.3	230.2	176.3	168	
24	PLACEBO	1	48.26	164.6	91.7	108.7	174.4	85.1	182.8	171.6	196.6	1181.4
	PLACEBO	2	47.5	160.6	88.2	111.5	159	77.6	180.8	132.5	127.7	
	PLACEBO	3	46.74	115	107.6	99.1	147.8	77.1	182.2	157.9	151.1	
	PLACEBO	4	46.99	131.2	71	105.4	163.8	77.7	181.4	169.9	168.3	
	CBD	1	48.77	149.4	89.8	112.4	186.7	78.2	197	158.9	149.4	1243.8
	CBD	2	46.48	115.2	74.5	94.5	171.2	73.5	174.8	133.2	130.1	
	CBD	3	45.97	94.9	59.5	81.7	139.1	68.5	164.6	129.7	119.6	
	CBD	4	48.77	141.2	85.5	109.6	174.5	77.4	181.5	151.2	148.9	
25	CBD	1	58.42	166.8	118.1	126.6	204.3	93.7	233.1	222.4	219.5	1936
	CBD	2	47.75	93.7	64.1	103.5	183	77.9	203.4	155.8	149.8	
	CBD	3	49.78	117	80.8	91.8	174.9	77	196.7	144.8	124.3	
	CBD	4	52.07	152.6	101.3	104.2	186.2	77	190.5	142.8	123.3	
	PLACEBO	1	55.37	134.5	83.3	130.6	222.6	88.1	217.9	209.6	192.5	685.4
	PLACEBO	2	53.59	128.2	74.8	121.3	218.2	81.2	204.2	177.4	168.3	
	PLACEBO	3	50.55	134.3	79.2	128.7	230	101.4	262.3	180.8	286.1	
	PLACEBO	4	51.31	152.5	106.3	140.7	230.9	101.7	259	219.2	195.9	
26	PLACEBO	1	34.04	105.7	66.1	66.7	100.7	53.1	94.7	170.1	161	1106
	PLACEBO	2	30.99	99.5	66.5	64.3	100.7	50	87.3	146.2	138.8	
	PLACEBO	3	32	91.9	63.4	78.1	126.4	48.8	93.9	155.7	152.1	
	PLACEBO	4	33.78	113.7	77.5	77.4	130.4	43.8	98.4	170.6	162.1	
	CBD	1	30.99	115.6	79.8	52	88.9	49.1	66	162.1	151.6	1511

	CBD	2	29.21	93.3	60.6	52.6	85.9	41.7	69.5	146.2	140.8	
	CBD	3	27.43	81	55.5	53.7	78.2	41.8	72.9	150.8	134.8	
	CBD	4	30.99	92	65.1	68.7	108.6	43.8	75.7	161.2	150.8	
27	CBD	1	41.91	180.3	115.3	115.4	135	95.5	197.6	211.4	192.4	727
	CBD	2	41.4	151.3	61.5	97	142.1	83.5	174.3	182.5	168.4	
	CBD	3	39.37	138.9	91.1	111.9	169.1	91.3	203.7	156	141.6	
	CBD	4	40.89	166	106.9	114.9	180.2	90	191.3	169.7	153.2	
	PLACEBO	1	46.23	129.9	80.1	108.5	153.1	78.3	151.7	189.8	174.5	524.8
	PLACEBO	2	43.94	118.1	78.2	98.3	135.6	64	120.3	147.6	122.8	
	PLACEBO	3	44.45	153.8	96.8	100.5	153.4	80.7	167.3	184.5	157.5	
	PLACEBO	4	43.94	167.6	92.2	83.4	118.5	48.8	104.6	181.2	174	

Raw Data

Inflammatory Markers

Partcipant	Trial	Time Point	IL-10	IL-1B	IL-6
1	CBD	1	6.92	1.92	3.52
1	CBD	2	8.33	3.06	4.48
1	CBD	3	7.9	3.01	4.36
1	CBD	4	6.73	1.76	3.89
1	PLACEBO	1	8.21	2.47	3.95
1	PLACEBO	2	6.98	2.09	3.54
1	PLACEBO	3	6.8	2.35	3.64
1	PLACEBO	4	10.09	3.3	5.22
2	CBD	1	6.92	15.96	5.55
2	CBD	2	9.06	19.81	7.37
2	CBD	3	7.35	16.49	6.87
2	CBD	4	7.41	17.88	6.72
2	PLACEBO	1	7.41	17.53	6.86
2	PLACEBO	2	7.5	16.74	6.61
2	PLACEBO	3	5.99	15.54	6.64
2	PLACEBO	4	7.99	17.76	7.3
3	PLACEBO	1	11.77	1.53	8.31
3	PLACEBO	2	12.66	1.45	7.87
3	PLACEBO	3	10.45	1.23	6.1
3	PLACEBO	4	10.87	1.26	5.62
3	CBD	1	8.69	1.33	5.89
3	CBD	2	11.59	1.29	7.33
3	CBD	3	16.34	1.16	7.2
3	CBD	4	N/A	1.24	5.71
4	CBD	1	12.45	1.42	<0.05↓
4	CBD	2	13.31	1.29	<0.05↓
4	CBD	3	15.24	1.48	<0.05↓
4	CBD	4	15.76	1.3	<0.05↓
4	PLACEBO	1	11.32	1.34	<0.05↓
4	PLACEBO	2	11.47	1.14	<0.05↓
4	PLACEBO	3	13.49	1.44	<0.05↓
4	PLACEBO	4	9.97	1.14	<0.05↓
5	PLACEBO	1	6.21	1.19	9.45

5	PLACEBO	2	5.93	0.97	8.71
5	PLACEBO	3	4.27	0.82	8.52
5	PLACEBO	4	6.36	1.13	9.52
5	CBD	1	5.13	1.36	7.76
5	CBD	2	4.7	1.17	9.22
5	CBD	3	4.75	1.89	11.11
5	CBD	4	5.09	3.62	9.76
6	PLACEBO	1	8.12	1.07	1.18
6	PLACEBO	2	3.53	1.39	0.33
6	PLACEBO	3	N/A	N/A	N/A
6	PLACEBO	4	4.95	0.93	0.69
6	CBD	1	2.21	0.99	1.01
6	CBD	2	5.26	1.21	2.37
6	CBD	3	2.21	0.95	0.52
6	CBD	4			
7	PLACEBO	1	7.58	1.25	3.41
7	PLACEBO	2	5.48	1.16	2.12
7	PLACEBO	3	9.82	0.63	0.35
7	PLACEBO	4	8.08	0.61	0.29
7	CBD	1	5.22	<0.49↓	<0.19↓
7	CBD	2	2.95	<0.49↓	<0.19↓
7	CBD	3	6.06	0.59	0.2
7	CBD	4	7.58	0.69	0.23
8	PLACEBO	1	7.77	0.6	0.24
8	PLACEBO	2	4.99	<0.49↓	<0.19↓
8	PLACEBO	3	6.6	1.55	19.11
8	PLACEBO	4	4.31	1.75	8.74
8	CBD	1	4.88	3.05	2.86
8	CBD	2	N/A	4.53	N/A
8	CBD	3	7.43	2.34	3.01
8	CBD	4	9.07	2.47	21.75
10	PLACEBO	1	7.18	1.58	16.83
10	PLACEBO	2	7.07	1.91	20.76
10	PLACEBO	3	8.04	1.03	0.52
10	PLACEBO	4	7.77	1.03	0.52
10	CBD	1	5.6	0.84	0.36
10	CBD	2	2.34	1.68	2.47
10	CBD	3	7.61	1.13	0.55
10	CBD	4	7.77	1.1	0.52

11	CBD	1	10.13	2.09	14.03
11	CBD	2	6.76	1.11	0.54
11	CBD	3	13.16	1.18	1.19
11	CBD	4	12.52	0.98	1.19
11	PLACEBO	1	12.36	0.93	0.98
11	PLACEBO	2	N/A	1.75	19.35
11	PLACEBO	3	4.07	0.8	<0.06↓
11	PLACEBO	4	N/A	1.28	N/A
12	CBD	1	N/A	1.29	2.13
12	CBD	2	8.05	1.45	1.84
12	CBD	3	11.21	1.67	1.74
12	CBD	4	N/A	1.2	1.56
12	PLACEBO	1	N/A	1.12	N/A
12	PLACEBO	2	N/A	1.19	1.7
12	PLACEBO	3	8.63	1.04	0.38
12	PLACEBO	4	7.85	1.12	0.43
13	PLACEBO	1	8.59	1.16	0.42
13	PLACEBO	2	8.01	1.13	0.37
13	PLACEBO	3	10.17	1.1	0.51
13	PLACEBO	4	8.24	1.12	0.41
13	CBD	1	8.87	1.04	0.38
13	CBD	2	12.16	1.13	0.52
13	CBD	3	2.91	1	2.8
13	CBD	4	N/A	0.8	0.85
14	CBD	1	3.42	0.85	1.18
14	CBD	2	4.31	0.71	1.19
14	CBD	3	N/A	0.9	N/A
14	CBD	4	N/A	1.02	N/A
14	PLACEBO	1	N/A	1.1	3.33
14	PLACEBO	2	3.16	1.03	1.63
14	PLACEBO	3	9.58	1.97	3.51
14	PLACEBO	4	7.85	2	3.01
15	PLACEBO	1	8.75	2.01	3.13
15	PLACEBO	2	6.45	1.7	2.5
15	PLACEBO	3	4.88	1.82	3.04
15	PLACEBO	4	N/A	1.93	3.63
15	CBD	1	7.46	1.88	3.55
15	CBD	2	3.46	1.54	1.46
15	CBD	3	5.07	0.94	1.35

15	CBD	4	5.07	0.98	1.34
17	CBD	1	5.56	1.02	1.57
17	CBD	2	6.68	1.05	1.34
17	CBD	3	3.2	0.64	0.6
17	CBD	4	N/A	0.41	0.44
17	PLACEBO	1	N/A	0.41	N/A
17	PLACEBO	2	11.62	0.6	0.35
17	PLACEBO	3	10.66	0.6	0.51
17	PLACEBO	4	11.11	0.64	0.47
18	PLACEBO	1	15.41	0.99	4.29
18	PLACEBO	2	14	1.09	4.21
18	PLACEBO	3	11.89	1.07	3.88
18	PLACEBO	4	14.2	1.27	4.28
18	CBD	1	10.56	1.1	4.59
18	CBD	2	11.25	0.92	4.59
18	CBD	3	12.74	1.21	4.72
18	CBD	4	8.19	1.26	N/A
19	PLACEBO	1	3.43	1.03	0.27
19	PLACEBO	2	3.19	1.09	0.17
19	PLACEBO	3	3.86	1.03	0.21
19	PLACEBO	4	10.39	1.11	0.56
19	CBD	1	3.69	1.03	0.51
19	CBD	2	N/A	1.08	N/A
19	CBD	3	4.27	1.17	0.62
19	CBD	4	2.99	1.06	0.51
20	CBD	1	5.54	1.28	0.17
20	CBD	2	N/A	0.98	N/A
20	CBD	3	5.85	0.93	<0.06↓
20	CBD	4	3.53	1.13	<0.06↓
20	PLACEBO	1	6.67	1.78	0.21
20	PLACEBO	2	5.23	1.46	0.12
20	PLACEBO	3	6.81	1.29	0.1
20	PLACEBO	4	5.98	1.47	0.16
22	PLACEBO	1	14.03	2.73	14.85
22	PLACEBO	2	N/A	2.63	N/A
22	PLACEBO	3	10.8	2.16	N/A
22	PLACEBO	4	11.62	2.35	17.28
22	CBD	1	19.71	2.59	11.89
22	CBD	2	23.28	2.75	15.46

22	CBD	3	17.95	2.5	N/A
22	CBD	4	15.81	2.49	8.04
23	CBD	1	6.43	0.68	0.19
23	CBD	2	5.61	0.64	0.48
23	CBD	3	6.95	0.67	<0.06↓
23	CBD	4	5.33	0.94	<0.06↓
23	PLACEBO	1	5.3	1.46	<0.06↓
23	PLACEBO	2	N/A	0.41	N/A
23	PLACEBO	3	N/A	0.32	<0.06↓
23	PLACEBO	4	4.88	0.71	<0.06↓
24	PLACEBO	1	5.23	2.84	<0.06↓
24	PLACEBO	2	5.57	1.49	<0.06↓
24	PLACEBO	3	4.54	1.26	<0.06↓
24	PLACEBO	4	4	1.61	<0.06↓
24	CBD	1	7.16	2.37	<0.06↓
24	CBD	2	7.74	1.39	<0.06↓
24	CBD	3	6.67	1.28	<0.06↓
24	CBD	4	5.16	1.35	<0.06↓
25	CBD	1	7.36	1.75	<0.06↓
25	CBD	2	6.05	0.31	<0.06↓
25	CBD	3	3.8	0.17	<0.06↓
25	CBD	4	5.26	0.31	<0.06↓
25	PLACEBO	1	4.95	1.35	<0.06↓
25	PLACEBO	2	5.92	0.53	<0.06↓
25	PLACEBO	3	5.23	0.22	<0.06↓
25	PLACEBO	4	6.26	0.62	<0.06↓
26	PLACEBO	1	N/A	1.3	N/A
26	PLACEBO	2	5.3	0.76	3.09
26	PLACEBO	3	N/A	0.52	N/A
26	PLACEBO	4	N/A	0.54	N/A
26	CBD	1	6.19	1.18	2.35
26	CBD	2	7.02	0.84	3.03
26	CBD	3	6.26	0.62	2.72
26	CBD	4	6.4	0.71	2.9
27	CBD	1	4.75	1.8	9.39
27	CBD	2	6.23	1.2	9.01
27	CBD	3	4.24	1.06	9.02
27	CBD	4	4	1.12	9.09
27	PLACEBO	1	7.43	2.74	13.37

27	PLACEBO	2	8.57	2.35	15.23
27	PLACEBO	3	6.88	2.15	15.54
27	PLACEBO	4			

APPENDIX E

IRB APPROVAL LETTER

Texas Woman's University
Institutional Review Board (IRB)
irb@twu.edu
https://www.twu.edu/institutional-review-board-irb/

April 16, 2020

Brett Crossland
Health Promotion & Kinesiology

Re: Initial - IRB-FY2020-244 The Effects of Cannabidiol on Markers of Performance Following Eccentric Exercise

Dear Brett Crossland,

The above referenced study has been reviewed at a fully convened meeting by the TWU IRB - Denton operating under FWA00000178 and approved on April 16, 2020. If you are using a signed informed consent form, the approved form has been stamped by the IRB and uploaded to the Attachments tab under the Study Details section. This stamped version of the consent must be used when enrolling subjects in your study.

Note that any modifications to this study must be submitted for IRB review prior to their implementation, including the submission of any agency approval letters, changes in research personnel, and any changes in study procedures or instruments. Additionally, the IRB must be notified immediately of any adverse events or unanticipated problems. All modification requests, incident reports, and requests to close the file must be submitted through Cayuse.

Approval for this study will expire on April 16, 2021. A reminder of the study expiration will be sent 45 days prior to the expiration. If the study is ongoing, you will be required to submit a renewal request. When the study is complete, a close request may be submitted to close the study file.

If you have any questions or need additional information, please contact the IRB analyst indicated on your application in Cayuse or refer to the IRB website at http://www.twu.edu/institutional-review-board-irb/.

Sincerely,

TWU IRB - Denton

APPENDIX F

MILLIPLEX MAP KIT PROCEDURES

All blood samples were collected using a 4 mL serum separator tube. Following collection tubes were inverted 5 times according to the manufacturer's suggestion. Samples were then allowed to rest between 30 and 45 min before being centrifuged. All samples were centrifuged at 1500 rpm for 10 minutes. Serum was then placed into a 1.2mL microtube and stored in a freezer at -80° until further analysis. A MILLIPLEX (Darmstady, Germany) Human High Sensitivity T Cell Magnetic Bead Panel was used to determine serum levels of IL-1β, IL-6, and IL-10. The following steps were taken as outlined in the manufacturer's instructions:

1. All samples and reagents were brought to room temperature.
2. 200 μL of wash buffer were added to each well. Plate was sealed and mixed on a plate shaker for 10 min.
3. Wash buffer was removed, and plate was dried by tapping smartly on paper towels.
4. 50 μL of standards and quality controls were added to the appropriate wells.
5. 25 μL of assay buffer was added to sample wells.
6. 25 μL of sample was added to sample wells.
7. 25 μL of Mixed beads were added to each well.
8. Plate was sealed and incubated on plate shaker for 16 hrs.
9. Well contents were removed and plate was washed 3 times with 200 μL wash buffer.
10. 50 μL detection antibodies were added into each well, plate was sealed and shaken at room temperature for 60 min.
11. 50 μL of streptavidin-phycoerythrin was added to each well.

12. Plate was covered and placed on plate shaker at room temperature for 30 minutes.

13. Well contents were removed and plate was washed 3 times with 200 μL of wash buffer.

14. 150 μL of drive fluid was added to each well.

15. Plate was sealed and placed on a plate shaker for 5 min at room temperature.

16. Plate was analyzed.

APPENDIX G

MYOGLOBIN ELISA KIT PROCEDURES

All blood samples were collected using a 4 mL serum separator tube. Following collection tubes were inverted 5 times according to the manufacturer's suggestion. Samples were then allowed to rest between 30 and 45 min before being centrifuged. All samples were centrifuged at 1500 rpm for 10 minutes. Serum was then placed into a 1.2mL microtube and stored in a freezer at -80° until further analysis. An Abnova (Walnut, CA) MB (Human) ELISA Kit was used to determine serum levels of myoglobin. The following steps were taken as outlined in the manufacturer's instructions:

1. All samples and reagents were brought to room temperature.
2. Serum was diluted 10-fold.
3. 20 μL of standards, diluted serum, and controls were dispensed into the appropriate well.
4. 200 μL of Enzyme Conjugate Reagent was dispensed into each well.
5. Plate was mixed for 30 sec and allowed to rest at room temperature for 45 minutes.
6. Incubation mixture was removed from well and placed in a waste container.
7. 100 μL of TMB Reagent solution was dispensed into each well and allowed to rest at room temperature for 20 minutes.
8. 100 μL of stop solution was added to each well and mixed for 30 seconds.
9. Absorbance was read at 450 nm with a microtiter well reader within 15 minutes.