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CANNABIDIOL (CBD) AND RESISTANCE TRAINING: DOES CBD ATTENUATE ACUTE PAIN?

Guillermo Pacheco

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Department of Kinesiology, Recreation, and Sport
Western Kentucky University
Bowling Green, Kentucky

By
Guillermo Pacheco

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Guillermo Pacheco

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DocuSigned by:
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Chair

DocuSigned by:
Danilo Tolusso
91D7499DC2C440C...
Committee Member

DocuSigned by:
Scott Arnett
A9127A7A9A39420...
Committee Member

Committee Member

DocuSigned by:
Jennifer Hammonds
EBE3858E068F42D...
Interim Director of the Graduate School

ABSTRACT

CANNABIDIOL (CBD) AND RESISTANCE TRAINING: DOES CBD ATTENUATE ACUTE PAIN?

INTRODUCTION: Resistance training (RT) is an advantageous form of physical activity for health and performance benefits; these benefits are maximized when done strenuously. However, strenuous RT can induce acute inflammatory pain which can lead to delayed-onset muscle soreness (DOMS). Common analgesics like non-steroidal anti-inflammatory drugs (NSAIDs) can block protein synthesis, so other alternatives are needed for exercise and athletic communities to maintain physiological adaptations. Cannabidiol (CBD) is a non-psychotropic cannabinoid with purported anti-inflammatory, anti-oxidative, and analgesic properties. One of the main reasons for the use of CBD in exercise is pain alleviation; however, research in humans is limited. Therefore, the purpose of this study was to evaluate two doses of CBD on acute pain after a single bout of strenuous RT. **METHODS**: Participants (n=10) completed a double-blind, crossover study for three weeks with a one-week washout between conditions. They ingested either a placebo, low dose (2mg/kg), or high dose (10mg/kg) two hours prior to the RT protocol, again eight hours later, and continued for 48 hours with two doses each day. Participants completed a strenuous RT protocol which included four sets of damage-inducing back squats. Pain was assessed with a Visual Analog Scale (VAS) and Pain Pressure Threshold (PPT) at baseline (before the first dosage), immediately after RT (to evaluate exercise induced hypoalgesia), then again at 24h, 48h, and 72h for each condition. Data for VAS was analyzed using 3x4 repeated measures ANOVAs for condition and time, and a 3x5 repeated measures ANOVA for PPT for condition and time. **RESULTS**: There was no significant interaction between condition and time for VAS pain ($F_{2.274, 20.464} = 0.382$; $p=0.713$; $\eta^2=.041$; N-B=.106).

There was also no significant interaction between condition and time for pain thresholds for any muscles tested in the study. **DISCUSSION**: The two doses of CBD do not appear to attenuate pain after a strenuous back squat protocol. In the current study, CBD does not seem to affect exercise-induced hypoalgesia and pain thresholds. The implemented RT protocol does not induce EIH. Future studies should consider increasing the sample size and include blood markers or other measures to accompany VAS and PPT measurements.

Key Words: Cannabidiol, pain, DOMS, exercise-induced hypoalgesia

I dedicate this thesis to my wife, Carla, my parents, Alexis and Lucy, and my siblings, Andrea, and Alec.

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CHAPTER I

THESIS INTRODUCTION

Resistance training (RT) is defined as any bodily movement exerted against a force with the purpose of improving skeletal muscle function (e.g., strength, power, hypertrophy). RT is generally recommended to practice regardless of training status or age (Faigenbaum et al., 1999). Leading organizations recommend that RT should address every major muscle group at least twice a week (American College of Sports Medicine, 2018). This recommendation is the minimum to prevent chronic, deleterious conditions and receive the health benefits of RT. Despite the known benefits of RT people might avoid it due to its ability to induce pain (Boutevillain et al., 2017).

RT can exacerbate pain in people living with chronic conditions (Arendt-Nielsen et al., 2011); however, it has been shown to promote exercise-induced hypoalgesia (EIH) in healthy populations. EIH is a period of time immediately after exercise where pain thresholds are higher than normal (Rice et al., 2019). On the other hand, RT can also cause soreness in people who are new or unaccustomed to exercise, termed delayed-onset muscle soreness (DOMS) (Cheung et al., 2003). DOMS is a painful sensation mainly caused by increasing the time under tension while lengthening the muscles, known as eccentric contractions (Hotfiel et al., 2018; Mizumura & Taguchi, 2015). This painful sensation is caused by inflammation in the active area, normally peaking at 24h-72h post exercise and can hinder movement and decrease performance for the days following exercise (Mizumura & Taguchi, 2015). Although this process is normal and necessary for muscular growth, some people might use non-steroidal anti-inflammatory drugs (NSAIDs) to decrease the discomfort. Although effective at decreasing inflammation and pain,

NSAIDs could hinder maximal muscular strength and growth by inhibiting pathways of protein synthesis (Schoenfeld, 2012).

Alternative remedies for DOMS have been increasing in popularity in the exercise and athletic communities. For instance, cannabidiol (CBD) is a non-psychotropic cannabinoid found in the sativa plant (Argueta et al., 2020). CBD has purported anti-inflammatory, anti-oxidative, and analgesic properties; however, research is limited on its efficacy in humans (Atalay et al., 2019). Some forms of CBD have been approved by the Food and Drug Administration (FDA) to treat chronic conditions like epilepsy and multiple sclerosis; however, little is known on the acute effects it has on pain (Samanta, 2019). Proposed mechanisms of action for CBD may be the antagonizing of the receptors of the endocannabinoid system (Laprairie et al., 2015; Thomas et al., 2009), influencing pain signals along neural pathways (Xiong et al., 2012), and attenuate inflammation by suppressing cytokine production and immune cell activation (Burstein, 2015). The endocannabinoid system may also play a role in modulating pain and EIH (Koltyn et al., 2014), so it would be important for research to investigate the role CBD has on acute pain after strenuous RT.

Overall Purpose and Study Significance

The purpose of this review was to investigate the current literature of pain and CBD in exercising communities. Secondary to the review, a study was developed to assess the efficacy of two different CBD doses on pain after a strenuous bout of RT. A secondary aim of the study was to analyze if CBD had an effect on the pain thresholds after strenuous RT protocol. To the authors knowledge, there is only one pilot study that assessed two CBD doses for pain (Stone et al., 2023), and no study examining the effect of CBD on hypoalgesia and pain thresholds in different muscles after a strenuous back squat protocol. The study has potential to add to the

limited literature of the usage of CBD and exercise, and to justify the usage and purported benefits of CBD in the athletic, exercise, and general communities.

Potential Limitations

- Non-invasive measurements to detect differences between conditions.
- Training adaptations outside the study from the participants.
- Subjective perception of pain.
- There is no standardized CBD dosage and timing.

CHAPTER II

Review of the Literature

This literature review begins with an overview of resistance training and three basic principles to maximize benefits. It is followed by a review of the performance and health benefits of resistance training. Next, the stimuli for resistance training adaptations are outlined. This section concludes with a comparison of high and low-load resistance training for muscular adaptations. A discussion about the definition and physiology of pain and perception is next. Following next is pain with resistance training and delayed-onset muscle soreness. An introduction to cannabidiol and its purported benefits are discussed next. This is followed by a summary of the physiological mechanisms of cannabidiol. Next, a review of the current research and use of cannabidiol in athletics and exercise. Timing of ingestion and dosing protocols for cannabidiol are detailed afterward. Finally, it concludes with safety considerations for the use of cannabidiol.

Resistance Training

Physical activity is defined as any movement in the body with skeletal muscles that will burn energy (Caspersen et al., 1985). It has been positively correlated with good overall health and increased quality of life (Gill et al., 2013); physical activity can be performed in different modes depending on an individual's preferences. General guidelines for physical activity from the American College of Sports Medicine (ACSM) are at least 150 minutes of moderate-intensity aerobic exercise per week and strengthening of all major muscle groups twice or more per week (ACSM, 2018). Resistance training (RT) is typically associated with goals to improve muscle hypertrophy and strength; however, RT also has added health benefits beyond increases in physical performance (Braith & Beck, 2007).

Inter-individual differences determine the impact of RT on the body; thus, RT programs should be individualized so that the model matches the individual (Kraemer et al., 2002). Regardless of the programming, RT has a positive relationship with muscle strength, hypertrophy, health, and other added benefits when practiced safely and appropriately (Hawley, 2008; Braith & Beck, 2007).

Performance Benefits of RT.

One of the most common benefits for individuals who perform RT is muscle strength (Kraemer et al., 2002; Sands et al., 2012). Muscle strength is the greatest amount of force that can be generated in one single muscle contraction (Kraemer et al., 2002). Untrained individuals have a greater capacity to benefit from RT compared to trained and elite athletes as the latter groups approach their physiological ceiling. However, no matter the age or training status, any RT is beneficial for the human body. Muscle strength is required for most sports to improve athletic performance (Suchomel et al., 2016). Even children can benefit from some type of RT if the practice is supervised and follows the correct guidelines; children can benefit from RT through an increase in muscle strength (Faigenbaum et al., 1999).

RT normally increases muscle strength, which can then promote muscle power. Muscular power corresponds to strength as it is related to the amount of force generated (strength) and the velocity of movement (Kraemer et al., 2002). RT increases the speed and velocity of muscle contraction, creating an ‘explosive’ movement (Macaluso & De Vito, 2003). Muscle power is essential for tasks requiring jumping, sprinting, or rapid changes of direction. In some sports, athletes need to kick or throw a ball which requires power for explosiveness. RT increases the rate of force development because training increases the speed at which force is produced

(Aagaard et al., 2002). RT increases the number of motor neurons recruited, which can create force faster than untrained individuals (Aagaard et al., 2002; Macaluso & De Vito, 2003).

Muscle hypertrophy is another positive consequence of RT as it induces muscle mass growth. More muscle mass means there is greater force and power potential of the muscle (Macaluso & De Vito, 2003). RT can also decrease body fat and increase lean muscle mass (Schoenfeld, 2010). This body composition scheme is a primary objective of athletes like bodybuilders who require big muscle mass and low body fat (Helms et al., 2015). Maintaining muscle hypertrophy can also assist with age-related losses in muscle mass, which can increase the quality of life, independence, and health benefits (Batista et al., 2014).

Health Benefits of RT

RT is most traditionally related to individuals who work out at training centers with heavy weights. However, concerns with the modern, mostly sedentary lifestyle have made researchers and the general population look into RT as a means for disease prevention and health promotion (Kraemer et al., 2002). For example, data from the Centers for Disease Control and Prevention (CDC) show the leading causes of death in America are chronic diseases such as heart disease, cancer, diabetes, and respiratory disease (CDC, 2022). Unintentional accidents are also included in that list, which includes falls. This is a concern for the elderly since they experience falls due to a decrease in muscle mass and bone density throughout the years. For this reason, researchers have looked into the benefits of RT for the general population.

Research has suggested that people lose 3-8% muscle mass every decade after 30 years of age, and even more after the age of 60 (Volpi et al., 2004). This reduction of muscle mass in old age seems to be attributed to a reduction in the number and size of muscle fibers (Evans & Lexell, 1995). However, research has suggested that RT can slow down the senescence of

muscle mass. Even though the reduction is inevitable with old age, people have positive adaptations from RT that attenuate the loss of muscle mass. Sustained muscle quality promotes a better quality of life for the individual (Schoenfeld, 2010; Volpi et al., 2004; Welle et al., 1996). RT also decreases the likelihood of individuals developing sarcopenia and weak muscles (Volpi et al., 2004). The risk of falls may be lowered through RT as it improves muscle strength and balance in older adults (Welle et al., 1996). Muscle strength and power could also lead to a higher rating of the quality of life as older individuals can be more independent (Macaluso & De Vito, 2003).

While muscle strength and hypertrophy are important benefits of RT, general health and disease prevention are arguably more important for an exercising individual (Gill et al., 2013). Heart disease is the leading cause of death in America (CDC, 2022), and the risk factors like high blood pressure, high cholesterol, inflammation, obesity, and diabetes (Kraemer et al., 2002). RT might be a good intervention for those wishing to reduce their risk for chronic diseases (Shailendra et al., 2022).

The prevalence of obesity in America is 41.9%, which increases the risk of heart disease and other health complications (CDC, 2021). Although diet is very important for weight loss, research has suggested combining dieting with RT is more effective than dieting alone (Miller et al., 2018). Positively, RT can control weight and prevent other comorbidities. Kraemer et al. (1999) found that dieting, aerobics, and RT lowered levels of body mass, fat mass, and low-density lipoprotein (LDL) cholesterol in individuals who were obese. Individuals who did aerobic exercise and RT also had better results in the strength and Wingate test performance (an anaerobic power assessment) when compared to participants who only dieted. One of the biggest concerns with obesity is the inflammation that causes disturbance to the cells over time. RT has

been associated with controlling inflammation levels in individuals who are obese as well (Vincent et al., 2006).

Hypertension, or high blood pressure, increases the risk of heart disease. High blood pressure is a reading ≥ 140 mmHg for systolic blood pressure, and/or ≥ 90 mmHg for diastolic blood pressure (CDC, 2020). Although aerobic exercise has mostly been associated with reducing blood pressure, research has suggested that RT can also be beneficial (Collier et al., 2008; Heffernan et al., 2013). This can be useful for those individuals that cannot perform aerobic exercise or would prefer RT. One concern is that RT may increase arterial stiffness; however, it seems that RT compensates for this mechanism by increasing vasodilatory capacity to lower blood pressure (Collier et al., 2008). Lowering blood pressure should reduce the risk of heart disease (Heffernan et al., 2013). Although some other factors and comorbidities affect heart disease, RT can also help manage overall good health.

Most experts would recommend a combination of exercise types for health promotion and disease prevention (ASCM, 2018; Caspersen et al., 1985; Gill et al., 2013). Nevertheless, research has suggested that RT alone can promote a healthy lifestyle. Learning the mechanisms behind the physiological adaptations of RT can lead to a better understanding of how to increase performance and health.

Stimuli for RT Adaptations

Athletes, bodybuilders, and powerlifters try to find the best approach to maximize the benefits seen from RT; understanding how it happens could lead to more targeted programming and better results (Schoenfeld, 2010). Muscle hypertrophy, which correlates to strength and power, normally occurs after many weeks of RT. The initial increase in muscle force potential is due to neural adaptations. These neurological adaptations are largely believed to be caused by

the recruitment and adaptation of motor neurons (Škarabot et al., 2020). RT adaptations can be achieved in different ways, but certain stimuli will promote optimal adaptations.

Hypertrophy is induced when the skeletal muscle is under tension (Gentil et al., 2006). Mechanical tension is the load or weight causing resistance against the working area. The sets, repetitions, and time under tension will cause protein breakdown and create a chain of events for muscle remodeling (Schoenfeld, 2010). Muscle remodeling can occur through the activation of satellite cells in muscle fibers, located between the basal lamina and the sarcolemma (Vierck, 2000; Toigo & Boutellier, 2006). Satellite cells in skeletal muscle are normally "dormant"; however, they become activated when mechanical tension is sufficient to stimulate a series of myogenic pathways (Schoenfeld, 2010).

Mechanical tension induces protein synthesis within the muscles. Protein synthesis is the creation of new proteins that can help build and repair muscle fibers following RT, which are activated by myogenic pathways (Zanou & Gailly, 2013). Myogenic pathways are a series of enzymes and proteins activated within a muscle to stimulate muscle growth (Le Grand & Rudnicki, 2007). These pathways further induce a greater synthesis-to-degeneration ratio, leading to muscle hypertrophy (Schoenfeld, 2010). When protein synthesis is activated, transcription and translation take place. Transcription is when genetic material is copied in the nucleus and converted from DNA to messenger RNA (mRNA). Translation occurs when the mRNA is transcribed to make a specific protein for muscle hypertrophy (Le Grand & Rudnicki, 2007; Zanou & Gailly, 2013).

One example of a myogenic pathway is insulin-like growth factor 1 (IGF-1), one of the anabolic hormones for protein synthesis (Toigo & Boutellier, 2006). Three isoforms of IGF-1 have been identified in skeletal muscle, systemic forms of IGF-1Ea and IGF-1Eb, and splice

variant IGF-1Ec. IGF-1Ec is also known as mechano growth factor (MGF), a variant that is believed to initiate muscle hypertrophy (Schoenfeld, 2010). MGF splices to the systemic IGF-1 forms; these forms can directly promote anabolic pathways for protein synthesis in myofibers. IGF-1 forms mobilize the gene for the activation of messenger RNA to stimulate protein synthesis for remodeling (Toigo & Boutellier, 2006). MGF promotes the activation of satellite cells and promotes their proliferation and differentiation (Vierck, 2000). IGF-1 can also activate the joining of satellite cells with myofibers which causes an increase in protein synthesis (Schoenfeld, 2010). Any activity, supplement, or drug that activates IGF-1 forms should result in protein synthesis.

Another attribute of RT that promotes hypertrophy, besides mechanical tension, is metabolic stress. Metabolic stress is the build-up of metabolites due to anaerobic glycolysis for energy production (Schoenfeld, 2010). The primary metabolites created after RT are lactate, hydrogen, and inorganic phosphate (de Freita et al., 2017; Schoenfeld, 2013). It is believed that an accumulation of these metabolites promotes adaptations to the skeletal muscle through hypoxia, reactive oxygen species (ROS), hormones, and cell swelling. These factors are related to starting anabolic pathways that activate protein synthesis and satellite cell proliferation (Pearson & Hussain, 2014; Schoenfeld, 2010; Schoenfeld, 2013).

Mechanical tension and metabolic stress are highly related to skeletal muscle adaptation secondary to RT. There are many ways to perform RT, however, research suggests that the maximum benefits are reached when exercising to promote metabolic stress and moderate mechanical tension (Schoenfeld, 2010). This is evidence to show that exercise selection is important when trying to get the most RT benefits.

High and Low-load Resistance Training

High-load RT (HL-RT) has been compared with low-load RT (LL-RT) to determine the best protocols for stimulating adaptations. According to the repetition continuum, which means the load needed for specific training, muscular strength adaptations occur in the 1-5 repetition range with high load, for hypertrophy 8-12 repetitions, and for muscular endurance, it is recommended more than 15 repetitions at a lower load (Sands et al., 2012). Generally, both HL-RT and LL-RT induce muscular strength and hypertrophy; however, research has suggested that HL-RT produces greater outcomes (Schoenfeld et al., 2017). HL-RT (≥70% of 1RM) has been often recommended by experts to promote skeletal muscle adaptations (Kraemer & Ratamess, 2004); yet, recent studies have suggested that muscular adaptations can be similar in different loading zones (Schoenfeld et al., 2021).

Studies have looked at the impact of LL-RT on muscle hypertrophy. Finks et al. (2016) examined the role of HL-RT and LL-RT in twenty-one young untrained participants performing unilateral bicep curls. They divided the participants into three groups: HL-RT, LL-RT, and a combination of both for eight weeks. They assessed pre and post-training muscle hypertrophy with the gold standard of measuring muscle cross-sectional area (CSA) with magnetic resonance imaging (MRI). After eight weeks they concluded that there was a significant increase in pre to post-training in CSA in all groups, but no difference between groups. It is important to note that LL-RT was trained to failure to have a similar response as HL-RT. The results of this study are similar to others in which LL-RT performed to failure promotes similar muscle hypertrophy in comparison with HL-RT (Lasevicius et al., 2019). Research says that training to failure induces metabolic stress for muscle hypertrophy in LL-RT, but training to failure has no significant effect on HL-RT (Lasevicius et al., 2019). It has been concluded that using LL-RT, the maximal

effort might be more important than the volume, hence, LL-RT is done to failure to promote hypertrophy (Fink et al., 2016; Lasevicius et al., 2019; Schoenfeld et al., 2017).

Although RT is beneficial, it is not always enjoyable as it can cause pain, discomfort, and soreness. Any type of RT is beneficial, but training should be specific to what the individual needs or wants (Schoenfeld et al., 2017; Sands et al., 2012). HL-RT benefits strength and size, while LL-RT done to failure can induce hypertrophy and endurance. Even LL-RT done to failure has been correlated with higher levels of rating of perceived exertion (RPE) and pain perception (Lasevicius et al., 2019). RT that causes pain could sometimes lead to less exercise enjoyment and lower levels of adherence to RT protocols for some individuals (Umeda et al., 2014). Methods that reduce sensations of pain during RT may promote long-term RT implementation.

Pain and Perception

The International Association for the Study of Pain (IASP) defines pain as, "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (IASP, 2020). Pain is a complex sensory and emotional feeling that can vary from person to person which can be differentiated by pressure, heat, cold, sharp, rough, etc. Pain is related to the first-person perspective of the individual (Treede, 2018) which differs from nociception, which is stimulus-related. Nociception is the neural activity by noxious stimuli that are processed through the central nervous system (CNS), specifically at the spinal cord level (St. John Smith, 2017). Pain is how a person interprets discomfort, or noxious stimuli, at the brain level. Noxious stimuli are sensed when the nociceptors, which are the receptors for pain, feel that there is an actual danger to the tissue (St. John Smith, 2017; Woolf, 2010). Nociception and pain can go hand in hand; however, there are instances where one could occur without the other.

The purpose of pain in humans is to protect from potentially harmful stimuli. One type of protective pain is nociceptive pain. This type of pain protects and causes a reaction to stay away from danger (e.g., recoiling from a hot object). Another type of protective pain is inflammatory pain, which is when pain is caused by injury or infection. The inflammatory system responds and sends inflammatory cells to the area which causes swelling and redness. Pain follows inflammation; however, this is adaptive and protective as it tells the body to stop doing the activity that caused the inflammation (Woolf, 2010). The third type is pathological pain, which differs from the other two as it has no real purpose. Pathological pain can be divided into neuropathic and dysfunctional pain. Neuropathic pain is normally caused by damage to nervous system tissue (e.g., spinal cord injury), but dysfunctional pain occurs when there are no clear signs of tissue damage or inflammation (St. John Smith, 2017). Pathological pain is maladaptive and worsens the perception of pain for someone (Brito et al., 2017). Strength training is most often associated with acute inflammatory pain due to the breaking down of muscle tissue; however, this leads to health benefits in the long term (Calle & Fernandez, 2010).

Pain can be classified as acute or chronic. Acute pain is normally caused by obvious tissue damage or pathology (Lavand'homme, 2011). On the other hand, chronic pain lasts longer than the normal healing timespan, and sometimes practitioners cannot determine what causes chronic pain (Arendt-Nielsen et al., 2011). Acute pain can transition into chronic pain if the problem persists, or the individual has the perception of ongoing pain (Woolf, 2010). Perception of pain is related to the experience of the person; pain tolerance is the maximum amount of pain that an individual can withhold, and pain threshold is the minimum amount to start causing pain (Edwards & Fillingim, 2007). Pain tolerance and threshold values are often used in pain-related literature.

Pain is often cited as a barrier to physical activity, and is the number one barrier for individuals with chronic low back pain (Sluka et al., 2013). Pain can decrease physical activity for individuals which can lead to more pain and other health complications (Brito et al., 2017). This could lead to a psychological cycle that causes more pain perception for the individual (Korff et al., 1996). RT may be a cause of acute and exacerbated chronic pain for some individuals; however, RT continues to be a useful exercise for decreasing the likelihood of developing chronic pain in the general population (Sluka et al., 2013).

Pain with Resistance Training

RT is commonly known as an effective treatment and prevention of chronic pain, which is established by regular exercise and physical activity (Brito et al., 2017; Sluka et al., 2013). In healthy populations, an acute bout of RT can promote exercise-induced hypoalgesia (EIH) (Focht & Koltyn, 2009; Koltyn & Arbogast, 1998). EIH is defined as a decrease in pain and pain thresholds after training activity (Rice et al., 2019). In other words, RT and other exercises can lead to a pain relief effect after an acute training bout. However, for individuals with chronic pain, RT might not have the same positive effect of EIH, compared with healthy individuals. Tools to assess pain have been developed for research and clinical purposes.

One tool to assess pain in patients is the visual analog scale (VAS). VAS is a visual test in which participants mark a vertical line on a 100mm (10cm) horizontal line, with 0 being no pain and 10 being the most unbearable pain (Scott & Huskisson, 1976). Evaluators then measure the vertical line and assess the patient's subjective perception of pain. VAS has shown reliability with acute pain instead of just chronic (Bijur et al., 2001). However, although VAS is an excellent tool to measure participants' subjective perception of pain, another tool with an objective measure can give valuable information as well (Mutlu & Ozdincler, 2015).

An acute bout of RT can aggravate the pain experienced by an individual with chronic pain. Lannersten and Kosek (2010) analyzed the hypoalgesia effect of exercise in healthy, shoulder myalgia, and fibromyalgia individuals. Pain pressure thresholds (PPT) were used to assess the pain thresholds for two different sites. This reliable tool is used to determine the effect of a treatment on musculoskeletal pain (Park et al., 2011) and is a reliable tool to measure acute and chronic pain in a patient (Mutlu & Ozdincler, 2015; Walton et al., 2011). It has been shown that for knee pain, the minimum detectable change in PPT is between 1.19 and 1.26 lb (Mutlu & Ozdincler, 2015). The participants in this study did isometric shoulder rotations and isometric knee extensions, and the researchers used PPT in these two muscle groups. They found an increase in pain thresholds in all sites for healthy individuals after exercise. In comparison, for the participants with shoulder myalgia, pain thresholds decreased in the shoulder, but increased in all other sites. However, participants with fibromyalgia experienced decreased pain thresholds in all areas (Lannersten & Kosek, 2010).

Throughout the literature, it seems that EIH is not very consistent and varies considerably in chronic pain individuals (Rice et al., 2019). It seems that a healthy population experiences a hypoalgesic effect of an acute bout of RT. On the other hand, people with chronic pain seem to experience EIH in areas that are not under constant pain. With knee OA, it seems to be that lower body RT can exacerbate the pain, but induce a hypoalgesic effect in the upper body (Burrows et al., 2014). However, someone with fibromyalgia has a high pain sensitivity due to RT (Lannersten & Kosek, 2010); this makes sense as someone with fibromyalgia experiences pain in the whole body. RT aggravating pain in individuals with chronic pain could lead to less physical activity which can make their situation worse. This could follow a cycle of not doing RT and

increasing pain due to inactivity. Finding different treatments to decrease pain caused by RT could increase adherence to exercise for people with chronic pain.

Delayed-Onset Muscle Soreness

Delayed-onset muscle soreness (DOMS) is the pain caused mainly by eccentric muscle action, new forms of exercise, or when someone is not accustomed to exercise (Cheung et al., 2003; Hotfiel et al., 2018; Mizumura & Taguchi, 2015). By definition, eccentric muscle actions create tension as the muscle lengthens, which is often implemented during RT exercise.

People practicing RT often experience DOMS if they are new to or doing unfamiliar RT. DOMS differs from the soreness experienced during exercise as symptoms for DOMS start after a "pain-free period" (Mizumura & Taguchi, 2015). DOMS can manifest as muscular pain or sensitivity to movement after exercise is complete (Haksever et al., 2016; Zhang et al., 2000), and can also decrease athletic performance as it presents with muscle stiffness and weakness (Cheung et al., 2003; Hazar Kanik et al., 2019). Pain caused by DOMS is typically at its peak 24-72 hours after exercise and is gone after, at most, seven days (Heiss et al., 2019; Mizumura & Taguchi, 2015). DOMS can occur for anyone, even elite athletes, who practice a new exercise or re-engage after a prolonged time of inactivity (Cheung et al., 2003). DOMS is an uncomfortable sensation for most, which could lead to a decrease in exercise enjoyment, adherence, and benefits of exercise. Although DOMS occurs often, the exact nature and mechanism have not been completely elucidated.

DOMS has been researched throughout the years and there have been different theories of why it occurs after a period of exercise. Some of the most common hypotheses include muscle damage, inflammation, lactic acid, and muscle spasms (Cheung et al., 2003). It is noted that eccentric exercise causes acute inflammation (Smith, 1991). Although muscle damage or acute

inflammation may be sufficient to induce DOMS, a recent study has suggested these are not the most detrimental aspects of exercise that can lead to DOMS (Mizumura & Taguchi, 2015). Some reasoning behind this proposal is that people have presented DOMS without muscle damage (Hayashi et al., 2016); alternatively, some people with muscle damage do not experience DOMS (Newham, 1988). Mizumura and Taguchi found in their animal models that eccentric contraction-induced DOMS can exist without any apparent muscle damage. These authors found two pathways involved in mechanical hyperalgesia (increased sensitivity to pain) including B2 bradykinin receptor-nerve growth factor (NGF) and cycloxygenase (COX)-2 glial cell line-derived neurotrophic factor (GDNF) (Mizumura & Taguchi, 2015). These factors are made by muscle fibers and satellite cells due to the action of lengthening the muscle under tension.

DOMS can affect daily life and athletic performance, potentially leading to people not accustomed to exercise to discontinue it or avoid it altogether. This is especially true with RT since it can lead to the exacerbation of DOMS for people new to eccentric contractions (Mizumura & Taguchi, 2015). For these reasons, researchers have looked at ways to prevent and treat DOMS. Studies have looked at the effectiveness of prevention and treatment using massage, Kinesio taping, cold and hot therapy, different exercises, and medication (Cheung et al., 2003; Farr et al., 2002; Heiss et al., 2019; Mizumura & Taguchi, 2015). The effectiveness of these treatments varies on timing and dosage. Mizumura and Taguchi (2015) explain that in theory, it would be possible to prevent DOMS by using B2 receptor antagonists, COX-2 inhibitors, anti-NGF antibodies, and anti-GDNF antibodies; however, only COX-2 inhibitors are available for human consumption. Common COX-2 inhibitors are non-steroidal anti-inflammatory drugs (NSAIDs) and are commonly recommended to help alleviate DOMS (Lewis et al., 2012). As explained by Cheung et al. (2003), the effectiveness of NSAIDs in the treatment

of DOMS varies on timing and dosage. If the treatment is taken before the occurrence of DOMS it completely blocks COX-2, but if taken after two days it fails to attenuate DOMS (Mizumura & Taguchi, 2015). However, there has been research suggesting that COX enzymes and COX-2 enzymes are important in the development of muscle hypertrophy (Schoenfeld, 2012). Blocking COX with NSAIDs could help with DOMS, but would prevent maximal muscle hypertrophy after RT (Bateman et al., 2023).

Since the pain can occur after an acute bout of RT, it is important to understand strategies to prevent and treat this pain without negatively impacting the benefits of exercise. Cannabidiol (CBD) has been rising in popularity among the population and athletic communities for its purported benefits; however, there is little research available to back these claims. CBD could play a role in reducing pain or discomfort secondary to exercise, or more specifically RT, by treating pain and inflammation without interfering with mechanisms that help individuals retain exercise benefits and maximize exercise enjoyment.

Cannabidiol

CBD is one of the main cannabinoids found in the Cannabis or sativa plant (Argueta et al., 2020); however, it does not have any psychedelic effects as other cannabinoids like Δ9-tetrahydrocannabinol (THC) (Leweke et al., 2012). The legal use of CBD has varied throughout the years in the United States and other countries. In the USA, cannabinoids that are extracted from marijuana are normally labeled Schedule 1 drugs, meaning they have no accepted medical benefits and can be abused (Corroon & Kight, 2018). There are three legal sources for CBD: parts of the Cannabis plant that are (1) not marijuana, (2) non-psychoactive hemp, and (3) industrialized hemp (Corroon et al., 2020). In 2018, the Food and Drug Administration (FDA) approved Epidiolex (CBD) as a treatment for certain seizure conditions and the federal

legalization of hemp has prompted pressure on the FDA to adjust regulations (Corroon & Kight, 2018; Corroon et al., 2020). These decisions have increased the usage of CBD among the general population, not limited to those suffering from chronic diseases.

CBD's purported benefits include being anti-oxidative, anti-inflammatory, analgesic, and possessing neuroprotective properties, each of which is compelling to athletes and the exercise community (Atalay et al., 2019; Booz, 2011; Close et al., 2021). The legal use of CBD in the USA and other countries has increased its usage and interest, but it has outpaced research (Rapin et al., 2021). One study found that one in four athletes report using cannabis (including CBD) within the past 12 months (Docter et al., 2020). Failure of the scientific community to keep pace with use can lead to misinformation and misuse, which could pose a risk of unknown side effects from overusing CBD (Argueta et al., 2020). Original research supporting CBD's purported health and performance benefits is poor and limited. There needs to be more research and education for CBD to use for exercise safely and effectively.

Physiological Mechanisms

For CBD to be used in the exercise and sporting context, it is necessary to understand the physiological mechanism of CBD on the human body; however, there is limited research on how it acts during and after exercise, specifically RT (Sahinovic et al., 2022). From what is known, the purported benefits of CBD are due to its interaction with the endocannabinoid system and its receptors (Ibeas Bih et al., 2015; Pertwee, 2008; Zou & Kumar, 2018). The endocannabinoid system is formed by a complex system of receptors and enzymes that help regulate the functions of the central nervous system (CNS) and peripheral nervous system (PNS) (Battista et al., 2012). The endocannabinoid system is made of two adenosine receptors of the G-protein coupled receptor family: (1) cannabinoid receptor type-1 (CB_1R) and (2) cannabinoid receptor type-2

(CB_2R) (Battista et al., 2012; Di Marzo & Piscitelli, 2015). Exogenous and plant-derived cannabinoids are said to interact with these receptors throughout the human body (Pertwee, 2008). CB_1R is known to help with homeostasis by enabling or inhibiting signals to different systems in the body and CB_2R (which has been less researched) is associated with inflammation and pain (Di Marzo & Piscitelli, 2015; Pertwee, 2008; Zou & Kumar, 2018). However, CB_1R and CB_2R, and the endocannabinoid system need more research to understand their mechanisms.

CB_1R and CB_2R receptors are more strongly associated with the most abundant cannabinoid found in plant cannabinoids, THC, but not with the other plant cannabinoids (Di Marzo & Piscitelli, 2015). The strong affinity of THC to the CB_1R receptor explains the psychotropic effects it has on the human body (Huestis et al., 2019). CBD has demonstrated low affinity to both receptors; however, research has shown that it can interact with the receptor in low concentrations (Pertwee, 2008). Research suggests that even though CBD has shown low affinity to the receptors, CBD acts in "high potency" as an antagonist to CB_1R and an inverse agonist to CB_2R (Laprairie et al., 2015; Thomas et al., 2009). CBD inhibits oxidative stress and inflammation by antagonizing the receptors that inhibit immune cell migration and reduces signs of inflammation (Lunn et al., 2005; Pertwee, 2008). However, there needs to be more research *in vivo* and in humans to understand the interaction of CBD with these receptors. There is no existing research on CBD and these receptors with exercise and RT. Future research should look into this since CB_1R and CB_2R could also have a potential role in acute and chronic pain after RT (Manzanares et al., 2006).

To the authors' knowledge, there is only one research study looking at the bioenergetics and physiology of CBD in an exercising body. This study did a randomized, double-blind study with nine endurance-trained males. The participants completed two running sessions, (1) a run

for 60 minutes at 70% VO2 max, and (2) an incremental run to exhaustion (Sahinovic et al., 2022). Sessions were separated by a washout period of seven days or more, and participants were assigned randomly orally CBD (300 mg) or placebo. The parameters measured were VO2, respiratory exchange ratio (RER), HR, blood glucose, lactate, RPE, and pleasure-displeasure measurement for the first run. For the incremental exhaustion run, VO2 max, RER max, and HR max were assessed. Although this was a pilot study, it had promising results for a larger research design. CBD appeared to increase VO2 and ratings of pleasure, as well as VO2 max and RER max compared to placebo. However, although CBD appeared to change some physiological aspects during aerobic exercise (VO2, VO2 max, RER max), the mechanisms behind it are not known. The authors do note that the endogenous cannabinoid, anandamide (AEA), appeared to be reduced in the presence of CBD (Sahinovic et al., 2022). AEA is the first endogenous cannabinoid discovered that binds with the body's endocannabinoid receptors CB_1R and CB_2R (Battista et al., 2012).

It is important to understand the physiological mechanisms of CBD in the human body since more people are using CBD in this context (Kasper et al., 2020). There are a few other studies using animal or human participants to analyze the effects of CBD on an exercising body. There needs to be more research on the acute benefits of CBD on RT and pain.

CBD in Athletics and Exercise

Physically active individuals often try to find strategies to increase performance and reduce soreness/pain. A common medication used to alleviate discomfort is NSAIDs. However, NSAIDs can have dangerous side effects when taken chronically and they have been shown to inhibit muscle growth (Bateman et al., 2023; Schoenfeld, 2012). An emerging alternative to NSAIDs is CBD. CBD's anti-inflammatory and analgesic properties may reduce soreness and

promote recovery after exercise (Argueta et al., 2020). A survey of 517 rugby players identified 26% of the sample had used CBD, with the main reason they reported using CBD was for pain and recovery. It is concerning that most of those in the study obtained information about CBD from the internet or another teammate (Kasper et al., 2020). There needs to be more research and reliable education accessible for the general population to make informed decisions. Being that the ACSM recommends exercise and RT to more than athletes (ACSM, 2009), CBD could have a potential role in pain and recovery in the general population as well.

Most available research on CBD and exercise is limited to animal studies (McCartney et al., 2020). It has been reported in preclinical rat models that CBD reduces immune cell activation (Klein et al., 2018; Ribeiro et al., 2012). CBD has also been shown to promote anti-inflammatory cytokines (e.g. interleukin (IL)-4, IL-10) (Weiss et al., 2008) and inhibit proinflammatory cytokines (e.g. IL-6, IL-8) (Arruza et al., 2017). Most of these studies have shown the anti-inflammatory response at higher CBD doses (≥ 10mg/kg); however, they are limited to animal models (McCartney et al., 2020).

RT and exercise can induce nociceptive, inflammatory, and acute and chronic pain (Cheung et al., 2003; Graven-Nielsen & Arendt-Nielsen, 2003). CBD may be an alternative to NSAIDs for its purported analgesic effects, but research is also limited in this area (Porter et al., 2021). Some research has evaluated the use of combined THC and CBD, which has promising results for its analgesic effects (Hoggart et al., 2014; Lichtman et al., 2018); however, CBD-only research for pain is scarce (McCartney et al., 2020).

Only a few studies are looking at biomarkers and physical performance after exercise and CBD supplementation in humans. Thirteen untrained males performed six sets of ten maximal eccentric repetitions at the elbow flexors followed by the consumption of 150mg of CBD oil

right after, and again after 24 hours (h), 48 h, and 72 h. Participants showed no significant results in perceived soreness, arm circumference, hanging joint angle, or peak torque (Cochrane-Snyman et al., 2021). However, this study performed "noninvasive" assessments which might not be sufficient or sensitive enough to detect the effect of CBD.

In contrast, Isenmann et al (2021) investigated the effects of a single CBD supplementation (60 mg Solubisat) on a back squat (1 RM BS), countermovement jump (CMJ), and blood serum concentrations of creatine kinase (CK) and myoglobin (Myo) before and after (24, 48, and 72h) a placebo-controlled crossover study. Researchers observed no significant effect of biomarkers and performance assessments; however, they observed small and significant results of lower CK and Myo concentrations after 72 h in the CBD group compared to the placebo (Isenmann et al., 2021). Similarly, 24 female athletes participated in a study to analyze the effects of CBD supplementation (5 mg/kg) on inflammation and performance after strenuous eccentric exercise (100 repetitions of unilateral leg extension). The researchers observed no difference in inflammation or performance (Crossland et al., 2022).

It is important to recognize that there may be different factors to consider for the effectiveness of CBD for analgesic and anti-inflammatory properties (McCartney et al., 2020). This includes how much inflammation and pain are induced and the dosage and timing of CBD ingestion. Most of the animal (Klein et al., 2018; Ribeiro et al., 2012) and human studies (Crossland et al., 2022; Isenmann et al., 2021) had different dosing protocols, which may have not been sufficient to detect the effectiveness of CBD following RT or exercise. This shows the importance of determining a dose for CBD for inflammation and pain that would be both effective and safe. A pilot human trial, with different CBD dosing protocols (2 mg/kg and 10 mg/kg) assessed pain and inflammation after an eccentric loading protocol; they found no

significant interaction between conditions and time. However, there was a visible increase in IL-6 at 48 h and 72 h after exercise in the placebo group that was not observed with low and high doses of CBD (Stone et al., 2023). These authors might have found statistical differences with a larger sample and assessing a larger portion of the body would be essential in future research to understand the effects of CBD after RT.

Timing and Dosing Protocol

Although CBD is not a new compound, research is lacking on the dosage protocol for CBD for exercise and pain. CBD intake can be administered in different ways (e.g. smoke, oil, topical, orally, gummies, etc.) (Close et al., 2021; Cochrane-Snyman et al., 2021; Hoggart et al., 2014). However, it seems that the most common form of ingestion is in capsules, vaporization, and oil (Larsen & Shahinas, 2020). Research on the bioavailability of CBD in human clinical trials is lacking, so there needs to be more research on the route of administration for CBD (Millar et al., 2018).

A recent systematic review analyzed the dosage and efficacy of CBD in human trials (Larsen & Shahinas, 2020). This systematic review used research from a variety of diseases like schizophrenia, anxiety, Crohn's disease, ulcerative colitis, dyslipidemia, nicotine addiction, and cannabis use disorder. The dosage from these studies varied from 300mg-600mg/day of CBD, and they were randomized controlled trials compared with a placebo. Some showed promising results with schizophrenia and anxiety patients; however, other diseases did not have any effect or could not be determined with the current CBD dosage. However, there is no dosage protocol for CBD in the treatment of acute or chronic pain. The authors highlight the importance of the impact of CBD on acute and chronic conditions (Larsen & Shahinas, 2020).

Although results from studies vary, some conclude that even low-dose of CBD in animal models attenuates pain and neuropathy (Casey et al., 2017; Costa et al., 2007); however, it is understood that animal models do not always translate to human participants (McCartney et al., 2020). In human participants, low doses of CBD seem to not attenuate pain or affect performance after high-intensity exercise (Cochrane-Snyman et al., 2021; Isenmann et al., 2021); as mentioned before; however, there is a lack of research in this area. To the authors' knowledge, there is only one pilot study assessing different dosages of CBD for pain and performance after eccentric exercise in humans (Stone et al., 2023).

Research notes that CBD ingested orally peaks in plasma concentration 1-3 hours after ingestion (Manini et al., 2015; Williams et al., 2021). It is also recommended to have a "washout" period of at least 72 hours between conditions (Williams et al., 2021). Researchers may consider modeling CBD dosage and timing schemes following the example of other exogenous substances.

Caffeine for Pain and DOMS

A substance that has been studied for similar purposes is caffeine (Hurley et al., 2013). Caffeine studies have looked at different dosages (e.g. low, moderate, and high) to treat pain and DOMS after high-intensity exercise (Astorino et al., 2011; Hurley et al., 2013; Spriet, 2014).

Research has determined that reduction in muscle pain by caffeine ingestion is dose dependent (O'Connor et al., 2004). In this study, researchers administered gelatin capsules which either had a high (10mg/kg) or moderate (5mg/kg) dose of caffeine compared to a placebo of an equal number. The results showed that caffeine had a significant linear effect on pain. The caffeinated participants showed a significant decrease in leg muscle pain compared to placebo, and the high dose had lower pain than the moderate dose (O'Connor et al., 2004). However, a

high dose of caffeine was approximately equal to consuming five 8-oz cups of coffee, which could have an adverse effect on some people as it is higher than the normal daily intake of caffeine (side effects include gastrointestinal upset, nervousness, mental confusion, and inability to focus) (Spriet, 2014). Therefore, most caffeine studies have determined a moderate dose of caffeine (5-10 mg/kg) ingested one hour before exercise is effective in decreasing pain perception and attenuates DOMS 24 h, 48 h, and 72 h after eccentric RT (Chen et al., 2019; Hurley et al., 2013; Maridakis et al., 2007). Low doses of caffeine are inconsistent and lack research on the effectiveness of decreasing pain and DOMS (Spriet, 2014).

Similar studies are needed for CBD as different dosing protocols may impact the benefits of analgesia, anti-inflammation, and anti-oxidative (Argueta et al., 2020). This is necessary as it will determine the effectiveness and safety of CBD for athletes and the exercise community, which may bring better results in recovery and performance (Close et al., 2021)

Safety Considerations

CBD is a substance that, like any other, should be regulated as the safety and health of individuals is of utmost importance. The benefit of CBD is that it does not have the psychotropic effect like other plant-derived cannabinoids as it contains less than 0.3% THC (Argueta et al., 2020). CBD has been used in preclinical and clinical trials for certain conditions like multiple sclerosis, chronic pain, and epilepsy with positive results for these conditions (Calabrò et al., 2020; Samanta, 2019; Villanueva et al., 2022). Patients in these types of groups seem to tolerate CBD well; however, there needs to be more research on the chronic use of CBD (Singh et al., 2022). Most available data on purified forms of CBD is from the medication Epidiolex®, which is an oral medication for intractable epilepsy (Huestis et al., 2019). Treatment for these conditions with Epidiolex® has come with positive results; however, there are some adverse

effects like tiredness, diarrhea, nausea, and hepatotoxicity (Close et al., 2021; Huestis et al., 2019; Samanta, 2019). Like with any other medication, the population should know that it may not be appropriate for everyone and that there is a lack of research available as it relates to the general population.

Although CBD has shown promising results in preclinical and clinical trials, it does not mean that it is completely safe for use (Close et al., 2021). There are many off-label CBD products available for purchase by the general public (Larsen & Shahinas, 2020). The lack of research on dose and timing is something the general population and others should take into consideration before consuming CBD. Research is also lacking with regard to exercise and RT-induced pain in humans; there should be more studies looking at the effects of CBD on acute pain and inflammation after RT since there is an increase in the use of CBD (Stone et al., 2023). Most studies looking at exercise and athletics use of CBD have not reported any adverse effects, but the research is limited to determining effectively the efficacy and safety of CBD for exercise and RT (Cochrane-Snyman et al., 2021; Crossland et al., 2022).

Conclusion

An emerging remedy in the exercise and athletic communities is CBD. CBD is the second most abundant cannabinoid in the cannabis plant but has no psychotropic effect on the human body compared to other cannabinoids (Argueta et al., 2020). It has purported benefits for anti-inflammation, anti-oxidative, analgesic, and neuroprotective properties; however, there is little research to be able to back these claims (Atalay et al., 2019; Booz, 2011; Close et al., 2021). Since there is an increased use of CBD among the general population, research must determine its effectiveness and safety. CBD could decrease pain, and inflammation, and increase exercise adherence and enjoyment among the population.

CHAPTER III

THESIS MANUSCRIPT

Introduction

Regular physical activity is recommended to maintain basic health benefits associated with movement (Brito et al., 2017). Many choose to engage in a form of physical activity termed resistance training (RT), which has health and performance benefits (muscular strength, endurance, and power) (Kraemer et al., 2002). RT helps stimulate protein synthesis to induce muscle growth, known as muscle hypertrophy (Schoenfeld, 2010). RT can prevent the risk of developing chronic diseases like osteoporosis, osteoarthritis, heart disease, obesity, and more (Welle et al., 1996). To obtain maximal benefits, RT is normally done with high-load few repetitions, low-load high repetitions, or a combination of both (Grgic et al., 2021). It is recommended that people practice some type of RT to maintain or improve health benefits. (Faigenbaum et al., 1999).

It is well established that RT is beneficial; however, RT can exacerbate pain for those living with chronic conditions. For instance, pain is the number one barrier to physical activity in those who live with chronic back pain (Brito et al., 2017). In healthy populations, RT has been shown to induce exercise-induced hypoalgesia (EIH), which describes the time frame after exercise where pain thresholds increase, meaning one can tolerate more pain post exercise compared to before exercise (Rice et al., 2019). Regular physical activity and exercise can decrease daily pain, and a single-bout of exercise can modulate pain thresholds and sensitivity (Koltyn et al., 2014). However, RT can also induce delayed onset muscle soreness (DOMS) after a training session, mainly in those who are unaccustomed to exercise (Cheung et al., 2003). DOMS is a painful and uncomfortable sensation that occurs after novel training, normally

peaking intensity 48-72 hours post-RT (Mizumura & Taguchi, 2015). DOMS is acute inflammatory pain that normally goes away within a week, but the painful sensation can decrease performance and physical activity for the days that follow the exercise bout (Hazar Kanik et al., 2019). Therefore, different treatments have been researched to alleviate the pain of exercise. Many might take non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain and inflammation associated with RT; however, NSAIDs can cause a decrease in maximal hypertrophy and strength after RT (Schoenfeld, 2012). For this reason, alternatives (cannabidiol, essential oils, etc.) have increased in popularity in exercise and athletic communities.

Cannabidiol (CBD) is a non-psychotropic cannabinoid found in the sativa plant. It is purported to have anti-inflammatory, analgesic, and anti-oxidative properties as well as reduce stress and anxiety (Argueta et al., 2020). CBD is known to interact through the endocannabinoid system with two receptors known as cannabinoid receptor type-1 (CB_1R) and cannabinoid receptor type-2 (CB_2R) (Di Marzo & Piscitelli, 2015). Research has found that CBD antagonizes these receptors which may inhibit immune cell migration and inflammation, potentially identifying how CBD could lead to a decrease in pain (Lunn et al., 2005; Pertwee, 2008). Furthermore, the mechanisms of EIH have not been fully understood, but it seems that the role of the endocannabinoid system might play a role in the nervous systems' pain perception (Rice et al., 2019). Research shows that there is an increase in levels of endocannabinoids after isometric exercise that lead to EIH (Koltyn et al., 2014). However, there has not been a study to look at the role of exogenous cannabinoids like CBD on EIH, which can have the potential of increasing pain thresholds after exercise.

CBD consumption has grown in athletic and exercise communities for its suggested benefits and for not impairing muscle hypertrophy and strength after training (Kasper et al.,

2020). However, most studies in humans have been designed to treat chronic conditions, so there is little research on the acute potential of CBD as an alternative for pain management. Most studies on exercise and CBD in humans have had mixed results, so there are no standardized protocols for the usage of CBD for acute pain after exercise (Crossland et al., 2022; Isenmann et al., 2021).

The field needs researchers to establish the efficacy and potential benefits of CBD due to its increase in usage. The main purpose of this study was to analyze if two different dosages (low vs high) attenuate pain after a strenuous back squat protocol compared to a placebo. A secondary aim was to identify differences between CBD and placebo with pain thresholds after a strenuous back squat protocol. We hypothesized that there will be a decrease in pain after CBD that is not witnessed with placebo. We also hypothesized that there would be an increase in pain thresholds with CBD after a strenuous back squat protocol compared to the placebo. Decreasing pain and soreness after RT could lead to greater exercise adherence and increasing volume of work to promote health and performance benefits of RT in the exercise, athletic, and general communities.

Methods

Participants and Anthropometrics

Participants were recruited from the greater Bowling Green, Kentucky community. To be included in this study, participants had to be recreationally active according to ACSM standards and healthy adults, as determined using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+). Additionally, they were required to have the capacity to back squat 100% of their body weight. Participants were excluded from the study if they were actively using CBD before the start of the study. Additionally, it was requested participants refrain from NSAIDs,

analgesics, caffeine, or any other supplement that has the capacity to attenuate pain. They were also told to avoid any other strenuous physical activity or exercise for the duration of the study. All procedures and the informed consent were approved by Western Kentucky University's IRB (22-229). A simulation analysis using previously collected pilot data (Stone et al., 2023) indicated the need for 15 participants to yield power the statistical analyses of .80 at an alpha of 0.05 for a mixed model ANOVA design.

After the participants were deemed eligible to participate in the study, they were asked to complete a baseline day which included familiarization to the protocol, the opportunity to ask questions, and freely fill out the informed consent. Next, the research team collected data on participant anthropometrics (body composition, height, and weight). Body composition was measured using a skinfold caliper by a trained evaluator (Lange Skinfold Caliper, Cambridge, MD). Height was assessed using a stadiometer (SECA, Hamburg, Germany) to the nearest 0.1 cm. Body weight was collected on a calibrated scale (COSMED, Concord, CA) with no shoes.

Exercise Protocol

Trial 0 of each condition represented baseline (BL), wherein participants performed a strenuous RT protocol to induce muscle soreness. To start up, they completed a standardized warm-up protocol with 5-10 minutes on a cycle ergometer, 20 butt kicks, 20 knee raises, 20 walking lunges, and 20 barbell squats with no added weight.

Participants completed four sets of barbell back squats at 60% of their body weight (Kabuki Strength Transformer Bar, Oregon, USA). The first two sets were to the maximum amount a repetitions a participant could do without failure. Sets three and four matched the number of repetitions they achieved in set number two. The rest period between each set was two minutes. Participants followed a cadence of 60 beats per minute (bpm) with four seconds down

(eccentric) and one to two seconds up (concentric). If, during sets three and four, the participants failed to keep form and/or was not able to keep up with the cadence, they were be asked to re-rack the barbell and rest for 30 seconds before completing the remaining repetitions. If participants failed, again they rested for another 30 seconds and attempted to complete the remaining repetitions; however, if they needed another rest then that set was terminated. Failure was determined as (1) proper technique was not maintained (thighs parallel to the ground), and (2) unable to continue repetition following cadence for two consecutive repetitions. Evaluators ensured participants followed the correct back squat form and cadence to the best of their abilities.

At the end of the squat protocol, evaluators monitored participants' physical condition while participants properly did a standardized cooled down by walking for 3-5 minutes and static stretching of major leg muscles for 30-60 seconds each. Participants returned to the lab 24, 48, and 72 hours later to have their pain assessed with all sessions taking place near the same time of the day (± 120 minutes). Participants performed the same protocol (matching volume) on trial 0 of each condition.

Cannabidiol

The study followed a double-blind, repeated measures crossover design adapted from the pilot study of Stone et al. (2023). Participants were randomized and counterbalanced into a placebo, low-dose (2 mg/kg), or high-dose (10 mg/kg) of CBD (CLoud N9ne CBD, Las Vegas NV). CBD oil and placebo were pipetted into capsules and the number of capsules was standardized across all conditions. At the baseline trial at the beginning of each week, participants consumed their first dosage at the end of their baseline measurements and a second dosage eight hours after the first. At trial 24h participants had another dosage after measurements

and a second dosage eight hours later. At trial 48h participants repeated the same dosing scheme as the day prior. At 72h trial, participants did not consume any dosage and had a one-week washout period. In total, participants ingested six doses throughout the week, and repeated the same consumption protocol with each condition.

Visual Analog Scale

The visual analog scale (VAS) measures a participant's perception of pain, and is represented by a 10cm horizontal line, with the two endpoints representing 0 (no pain) and 10 (pain as bad as it can be) (Bijur et al., 2008; Scott and Huskisson, 1976). Upon arrival, participants were told to mark a vertical line on the scale where they thought their current state of pain in the lower extremities was at the moment. Participants marked VAS at baseline, 24h, 48h, and 72h after the back squat exercise protocol. VAS scores were determined by measuring the horizontal line from the start (no pain) to the vertical line marked by participants in cm.

Pain Pressure Threshold

Pain pressure threshold (PPT) was measured using a handheld digital algometer (Wagner FDX-25, Wagner Instruments, Greenwich, CT) that records the linear force applied between 0-100 N. The algometer has a 1-cm^2 round rubber tip, and values are shown as the maximum force applied before the individual verbally stated that the pain threshold has been reached.

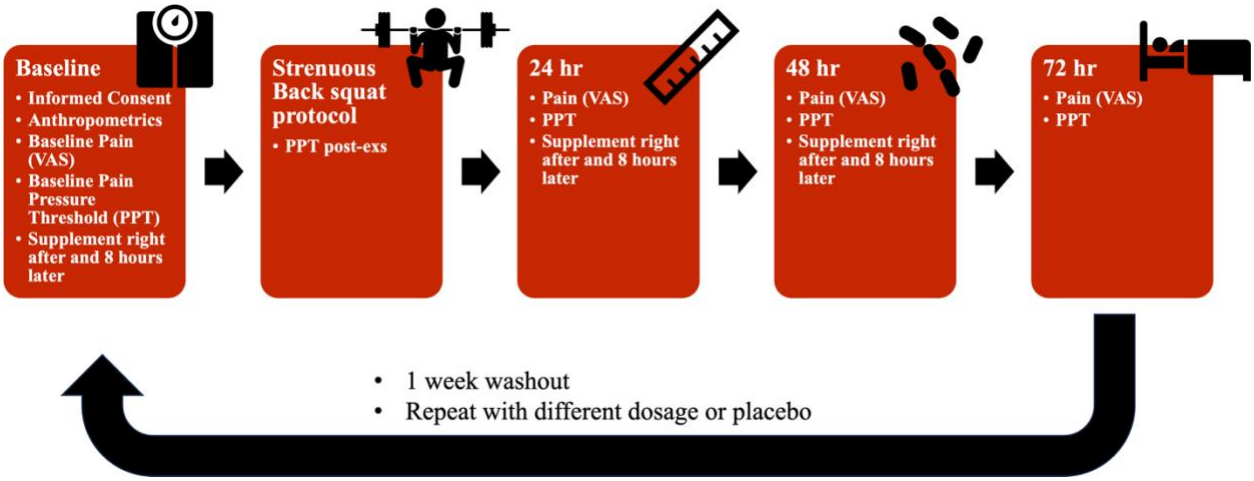
The following standardized protocol was used when evaluating participants. First, participants were familiarized with the evaluation tool. An initial PPT measurement was taken on the hand to ensure the participant knew how to differentiate between their report of tactile and painful stimuli. The following instructions were used; “I am going to begin applying pressure in your muscle. I want you to tell me the moment the sensation changes from comfortable pressure to slightly unpleasant pain” (Walton et al., 2011). Pressure was applied perpendicular to the skin

at a rate of 5 N/s at the different sites of interest, described below. We then asked the participants to say “stop” as soon as they differentiate pressure from pain, which signaled for the algometer to be immediately released.

PPT was assessed bilaterally (“L” for left and “R” for right) at the muscle belly of the Vastus Lateralis (VL), Vastus Medialis (VMO), Gluteus Maximus (GM), and Biceps Femoris (BF). Muscles were palpated and measured by a trained evaluator. The site for the VMO was five cm proximally from the superior medial border of the patella. The VL was one-third proximal from the distance of the superior lateral border of the patella and the greater trochanter. For the GM, the site was one-third of the proximal distance from the posterior superior iliac spine to the greater trochanter. Lastly, BF was one-third distally from the ischial tuberosity to the head of the fibula. Sites were marked on the skin with a permanent marker so that measurements were consistent each day PPT was taken. PPT was assessed before the exercise protocol, 5 minutes after the protocol, and then after 24h, 48h, and 72h post-protocol for each participant in each condition. Evaluator took the mean of three measurements of PPT for each site on each side of the body. Evaluators rotated measurement sites (VMO, VL, BF, GM) with a one-minute rest after a completion testing all eight muscles. Each measurement was blinded to the participant and was taken in a relaxed state in a supine or prone position according to muscle positioning. Summary timeline of events is in Figure 1.

Figure 1

Timeline of Events



Statistics

To detect the effects of CBD dosage on pain with response to strenuous RT, a 3 (condition) x 4 (time) repeated-measures analysis of variance (ANOVA) was performed for the VAS. When appropriate, pairwise comparisons were made by comparing timepoints back to baseline values using Bonferroni correction. Therefore, post-hoc comparisons for the VAS were assessed at $\alpha < 0.0125$ (0.05/4). Assumptions of normality of residuals were assessed via visual inspection of QQ plots. Mauchly's test was also used to assess the assumption of sphericity with a Greenhouse-Geisser correction applied to the degrees of freedom if the assumption is violated. Effect sizes are presented and calculated as partial eta squared ($\eta p2$). Statistical significance was set at $\alpha < 0.05$.

To determine the effects of the intervention on PPT, a 3 (condition) x 5 (time) repeated-measures ANOVA was calculated to detect differences between conditions in the different muscles tested outlined in the methodology. When appropriate, pairwise comparisons were made by comparing timepoints back to baseline values using Bonferroni correction. Therefore, post-hoc comparisons for PPT were assessed at $\alpha < 0.0125$ (0.05/4). All data were analyzed using

SPSS (v29.0, IBM Corp., Armonk, NY, USA). Data is presented using means ± standard deviation (SD) unless otherwise stated. Statistical significance was set at $\alpha < 0.05$.

Results

Participant (n=10, 7 men and 3 women) demographics are presented in Table 1.

Table 1

Participant Demographics

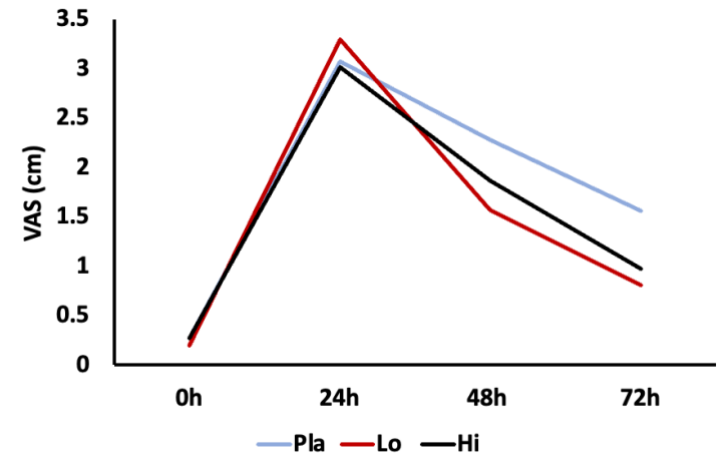
	Mean	Standard Deviation
Age (yrs)	20.6	2.12
Height (m)	1.73	0.1
Weight (kg)	73.12	14.14
BMI (kg/m^2)	24.14	3.21
Fat Mass (%)	13.24	6.01

Visual Analog Scale

To address any deviations from the sphericity assumptions, a Greenhouse-Geisser correction was applied to the degrees of freedom of the error and model terms. A repeated measures ANOVA revealed that there was no significant interaction between condition and time on VAS pain ($F_{2.274, 20.464} = 0.382$; $p=0.713$; $\eta^2=.041$; N-B=.106). No significant main effects were found for condition ($F_{1.26, 11.344} = 0.227$; $p= 0.698$; $\eta^2=0.025$; N-B=0.074), but were significant for time ($F_{1.688, 15.191} = 22.686$; $p < 0.001$; $\eta^2= 0.716$; N-B= 1.0). Post-hoc pairwise comparisons revealed that VAS pain was significantly lower at baseline compared to 24h and 48h, but not at 72h. Visual representation of VAS results are presented in Figure 2.

Figure 2

Visual Analog Scale Across Study Duration



Pain Thresholds

A repeated measures ANOVA revealed no significant interaction for pain thresholds for condition or time for any muscles tested. There were no significant main effects for condition for any muscle. Significant main effects for time were found in LVMO, both VL, both BF, and LGM. Post-hoc pairwise comparisons of main effects on the time component in RBF showed pain thresholds to be significantly different post-exercise ($p = 0.005$), 48h ($p = 0.007$), and 72h ($p = 0.003$), compared to baseline. For LBF, pairwise comparisons presented a difference at the 72h mark ($p = 0.004$), compared to baseline; however, for the other muscles showing a significant for the main effect of time, no other time points were significantly different compared to baseline. Results are outlined in Table 2. Visual representation of pain threshold muscles are in Table 3.

Table 2

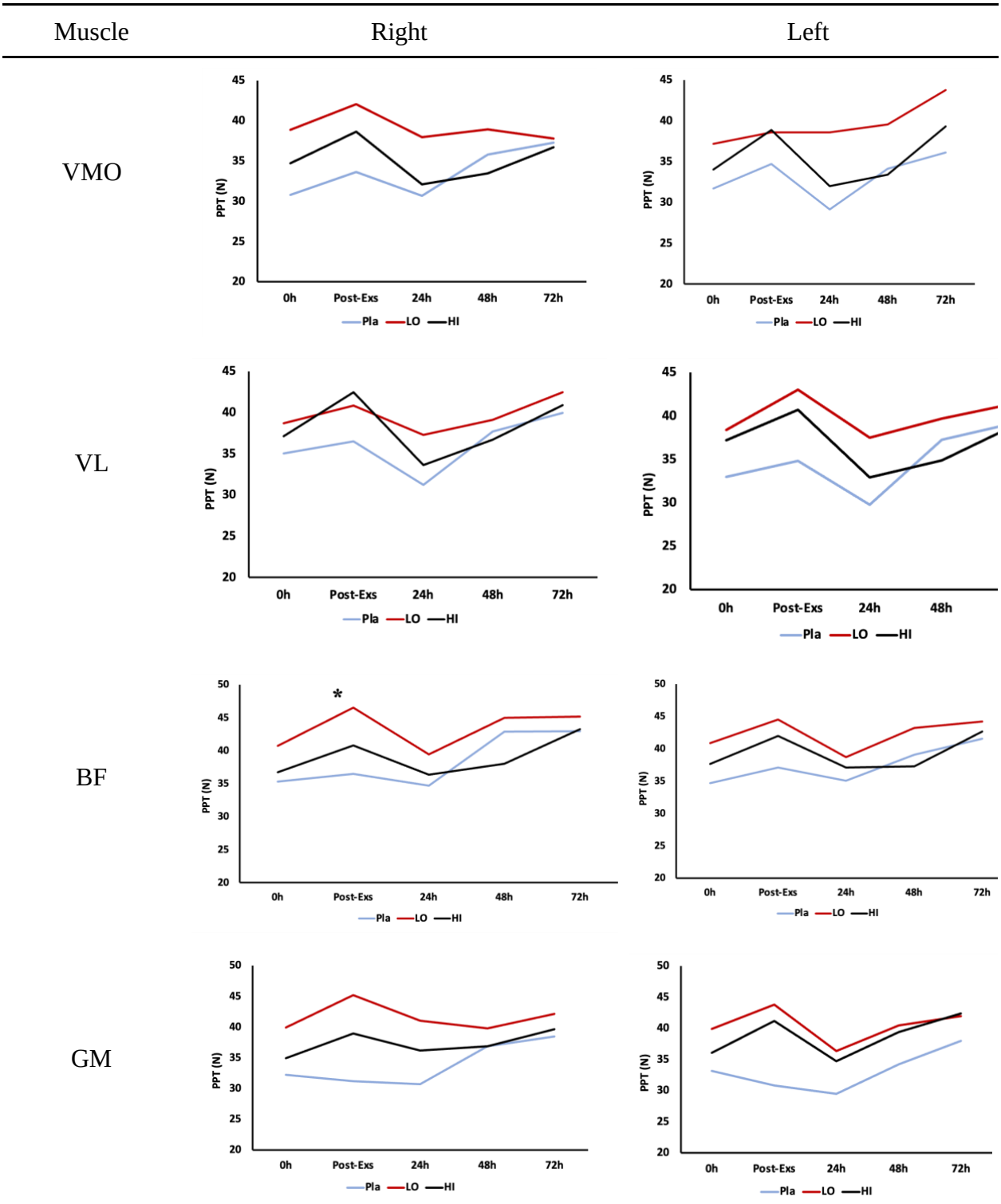
Pain Threshold test statistics, p-value, and partial-eta squared

	Condition			Time			Condition x Time		
	F	*p*	η_p^2	F	*p*	η_p^2	F	*p*	η_p^2
RVMO	0.776	0.425	0.079	2.580	0.110	0.223	1.740	0.179	0.162
LVMO	1.114	0.333	0.11	3.956	0.038*	0.305	1.125	0.359	0.111
RVL	0.358	0.615	0.038	5.356	0.012*	0.373	0.470	0.661	0.050
LVL	0.727	0.450	0.075	5.048	0.015*	0.359	0.96	0.402	0.096
RBF	0.721	0.447	0.074	7.425	0.002*	0.452	1.017	0.378	0.102
LBF	0.575	0.503	0.06	5.041	0.009*	0.359	0.511	0.611	0.054
RGM	1.179	0.314	0.116	2.665	0.078	0.228	1.448	0.260	0.139
LGM	1.352	0.279	0.131	6.562	0.003*	0.422	0.902	0.446	0.091

Note. * Denotes significance at the 0.05 alpha level.

Figure 3

Pain Thresholds across study duration



Note. * Denotes significant EIH post-exercise.

Discussion

The primary purpose of this investigation was to determine if different dosages (low and high) of CBD attenuated pain after a strenuous back squat protocol compared to placebo. With the current sample size (n=10) results revealed that there were no significant differences between conditions across time; therefore, there was no difference in pain reduction between CBD doses and placebo after a strenuous back squat protocol. A secondary purpose was to analyze if different dosages of CBD impacted pain thresholds in different lower leg muscles after strenuous back squat protocol compared to placebo. There was no difference in PPT between CBD and placebo. However, the investigation does determine that consuming high (10ml/kg) and low (2ml/kg) doses of CBD is safe for a generally healthy population as no adverse events were recorded.

We hypothesized that CBD would decrease pain sensation compared to placebo; however, there was no significant difference at any time point with the current results. These results are similar to other research looking at the effects of CBD with RT using subjective pain scales (Cochrane-Snyman et al., 2021; Crossland et al., 2022). Similar to other studies (Cochrane-Snyman et al., 2021; Crossland et al., 2022; Stone et al., 2023), we expected to see differences in the time across study duration after intense eccentric RT (Mizumura & Taguchi, 2015). Research shows DOMS peaks at 24h-72h after a strenuous bout of RT (Heiss et al., 2019; Mizumura & Taguchi, 2015). We found that DOMS peaked at the 24h and 48h mark compared to baseline measurements using subjective pain. To reiterate, this study recruited recreationally active adults who had not gone through extensive eccentric focused RT. The current back squat protocol seems to be sufficient to cause pain in recreationally active young adults in the lower legs for up to 48h after the RT. However, that pain seems to deteriorate at the 72h mark.

To the authors knowledge, this is the first study looking at the effects of different CBD dosages on pain thresholds and EIH. We hypothesized that post-exercise pain thresholds would be higher in the CBD conditions compared to placebo. However, we did not detect significant EIH in any condition in this investigation. The exact mechanisms of EIH are not established completely; however, research has shown that the endocannabinoid system could play a role in pain thresholds after exercise as it increases endocannabinoid receptors and its ligands (Koltyn et al., 2014). CBD seems to antagonize the endocannabinoid receptors and inhibit inflammatory cell response (Lunn et al., 2005; Pertwee, 2008), so cannabinoids could potentially play a role in EIH and regulation of pain thresholds.

Results revealed that there was no increase in pain thresholds after the strenuous back squat protocol. Other research shows that a single bout of exercise can induce EIH and increase pain thresholds (Focht & Koltyn, 2009; Koltyn & Arbogast, 1998; Koltyn et al., 2014). Our findings did identify that there was a significant difference for time for LVMO, both VL, both BF, and LGM muscles. Post hoc analysis revealed that when comparing time points to baseline, LBF at the 72h mark was significantly higher. RBF had significantly higher post-exercise, 48h, and 72h marks compared to baseline. EIH only occurred in the RBF muscles as pain thresholds was higher post-exercise compared to baseline. These results might suggest that the current back squat protocol was not sufficient to induce EIH and increase pain thresholds.

One novel component of the study is that it focused on only one exercise to induce muscle damage which was on eccentric movement based. Other studies, although strenuous (75% of 1RM), did multiple exercises of RT which were equally concentric and eccentric movement (Focht & Koltyn, 2009). Additionally, other studies have shown the effect of EIH after three minutes of a single RT exercise (Koltyn et al., 2014), so EIH can happen with a single

exercise like in the current study. This could suggest that EIH is mediated by movement or exercise type (e.g., concentric rather than eccentric, BFR, whole body). We could only identify EIH in RBF; however, trends of Figure 3 might show that EIH could occur in other muscles which could be detected with a larger sample size. We expected to see an increase in pain thresholds post-exercise in each muscle; however, this only occurred in the RBF. Some proposed mechanisms of EIH include increasing endogenous opioids, serotonin, and endocannabinoid receptors (CB_1R and CB_2R) after exercise (Lima et al., 2017). CBD has an affinity to endocannabinoid receptors as an antagonist which could lead to block immune cell migration to reduce pain and inflammation (Lunn et al., 2005). This could mean that CBD could have a negative impact on EIH; however, it seems that the low dosage could increase pain thresholds compared to placebo. Future studies could investigate to see the physiological effects of CBD on EIH and endocannabinoid receptors. It would be also necessary to investigate CBD with other modes of exercise like blood flow restriction training, which is known to have a higher hypoalgesia effect than traditional training potentially due to metabolic stress (Hughes & Patterson, 2020).

One of the study's main limitations was the small sample size. Visual inspection of VAS data (Figure 2) indicates that CBD might attenuate acute pain regardless of dosage; however, a small sample size might not be sufficient to detect significant differences. Most studies with CBD and exercise have been done with small sample sizes which can be a limitation in finding any significant changes between conditions (Cochrane-Snyman et al., 2021; Crossland et al., 2022; Stone et al., 2023). As mentioned before, only the RBF muscle had significant EIH immediately after the back squat protocol; however, a visual inspection of the other muscles (Figure 3) may suggest that these hypoalgesia effects immediately after the strenuous protocol

might have occurred but were statistically not detected. It seems possible that CBD could play a role in pain thresholds, though a larger sample would be necessary to expose this phenomenon. There is a trend that the low dose CBD condition may have contributed to higher pain thresholds when compared to placebo and the high dose conditions; however, more research is needed to determine this effect.

Another limitation to this study might be that the measurements implemented were non-invasive in nature. Taking blood samples to assess inflammatory markers (e.g., myoglobin, interleukin-6, and interleukin-10) to see how they correlate with a subjective pain scale might give a more accurate perspective on CBD's influence on pain (Stone et al., 2023). Similarly, analyzing activity levels of endocannabinoid receptors (i.e. CB_1R and CB_2R) and ligand activity (e.g. anandamide) after an intense bout of exercise could determine the effect that CBD has on EIH and pain thresholds (Koltyn et al., 2014). However, given the monetary and time cost of utilizing invasive measurements, VAS and PPT are validated, and reliable measures used to assess pain after our strenuous bout of RT (Bijur et al., 2001; Park et al., 2011).

Future studies should implement other exercise modes to see the physiological effects of CBD. Research on humans with CBD and exercise is limited, so it is imperative that scientists continue their investigation into CBD to justify its usage in healthy exercising communities. Simulation data using the current results of the study reveal that doubling the sample size for pain thresholds would be necessary to power the statistical analyses of .80 at an alpha of 0.05. Increasing the sample size and using more sensitive measurements to detect changes could strengthen the results, as non-statistical trends have shown that CBD may attenuate pain after strenuous exercise. Our sample of recreationally active young adults also limits the application of our findings; noting this, more research is needed in different types of populations (varying age,

disease status, training status, etc.). Furthermore, there is no standardized dose for CBD, so future investigators may implement different dosage (absolute quantities rather than ml/kg) and timing protocols to attenuate pain and inflammation after exercise. Due to the increase in CBD usage, the results of this study should perpetuate the need to do more research on CBD and exercise.

Visual inspection of the VAS and PPT shows the low dosage of CBD had a greater impact at attenuating pain compared to high dose and placebo. Future studies should look into the threshold in which a high dosage of CBD might not help in attenuating pain or inflammation. Like other drugs, too much of a substance could have an opposite effect on its purported benefits and side effects dangerous to the human body (Davis & Robson, 2016). Nevertheless, the current dosage scheme seems safe for the human body, but the low dosage of CBD might have a greater impact at attenuating pain.

Conclusions

Although CBD did not statistically impact acute pain or produce pronounced EIH, it was safely administered at both a low and high dose in recreationally active young adults. There do appear to be visual trends of CBD improving both pain and EIH, but the small sample size limits our ability to detect these differences. At this time, the authors cannot make a recommendation for or against the implementation of CBD.

CHAPTER IV

THESIS CONCLUSIONS

The current study expands upon the CBD and exercise literature. While other studies have looked at only one dose, the current study expands upon two different dosages (low and high) of CBD. Participants also ingested CBD two hours prior to the strenuous back squat protocol, and from the author's knowledge there is only one other study that did a similar timing scheme (Crossland et al., 2022). To the authors' knowledge, this is the first study looking at pain thresholds with CBD and exercise. Although the current study did not find any significant effect of CBD on acute pain after a strenuous bout of RT, future studies should focus on increasing sample size, implementing more sensitive, albeit invasive measurements, different sample populations, and the safety of CBD on the human body. In the current study, it seems that the back squat protocol was sufficient to cause DOMS and pain for up to 48h compared to baseline; however, different exercise modalities should be assessed as well to research the efficacy of CBD across exercise modalities.

DOMS and acute pain can happen after RT, and although the current study does not support CBD as a way to attenuate pain, RT should still be a common practice for everyone. Traditional RT (equal concentric to eccentric phases) can increase pain thresholds after a single bout of exercise (Rice et al., 2019). Consistent RT can lead to improved pain management, prevent chronic pain, and increase quality of life over the lifespan (Kraemer et al., 2002). Scientists still need to research the potential anti-inflammatory, anti-oxidative, and analgesic properties CBD has on the exercising body to determine its efficacy and safety.

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Appendix A

INSTITUTIONAL REVIEW BOARD
OFFICE OF RESEARCH INTEGRITY

DATE:	January 17, 2023
TO:	Whitley Stone, PhD
FROM:	Western Kentucky University (WKU) IRB
PROJECT TITLE:	[1887256-2] Cannabidiol (CBD) and Eccentric Resistance Training
REFERENCE #:	IRB# 22-229
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	January 17, 2023
EXPIRATION DATE:	January 17, 2024
REVIEW TYPE:	Expedited Review

Thank you for your submission of Continuing Review/Progress Report materials for this project. The Western Kentucky University (WKU) IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a project design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding followed by a *signed/implied* consent form. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

This project has been determined to be a MINIMAL RISK project. Based on the risks, this project requires continuing review by this committee on an annual basis. Please use the appropriate forms for this procedure. Your documentation for continuing review must be received with sufficient time for review and continued approval before the expiration date of January 17, 2024.

Please note that all research records must be retained for a minimum of three years after the completion of the project.

If you have any questions, please contact Robin Pyles at (270) 745-3360 or Robin.Pyles@wku.edu. Please include your project title and reference number in all correspondence with this committee.

INFORMED CONSENT DOCUMENT

Project Title: Cannabidiol (CBD) and Resistance Training

Investigators:
Whitley Stone, PhD; whitley.stone@wku.edu
o: 270-745-4321; c: 270-202-8546;

Danilo Tolusso, PhD; danilo.tolusso@wku.edu
School of Kinesiology, Recreation, and Sport

Guillermo Pacheco; andres.pacheco969@topper.wku.edu

Karen Mason, PhD; karen.mason@wku.edu
Applied Human Sciences

You are being asked to review this project conducted through Western Kentucky University. The University requires that you give your signed agreement to allow the volunteer below to participate in this project.

Volunteer's Name: _____ **Phone Number:** _____

The investigator will explain to you in detail the purpose, procedures, and the potential benefits and possible risks of participation. You may ask any questions you have to help you understand the project. A basic explanation of the project is written below. Please read this explanation and discuss with the researcher any questions you may have.

If you then decide to approve participation in the project, please sign this form in the presence of the person who explained the project to you. You should be given a copy of this form to keep.

1. **Nature and Purpose of the Project:** We plan to investigate if there is any effect of cannabidiol (CBD) oil (a high and low dose) on the inflammatory response seen after resistance training (RT). We will measure this inflammatory response through discomfort you feel, markers in your blood, and your muscle function.

2. **Explanation of Procedures:** Before we can enroll you in the study, we will decide if you are qualified. You must meet the age requirement (18 years of age or older), weigh at least 110 pounds, have performed resistance training in the past five years, you must feel healthy (absence of disease, flu, cold, fever, etc.), you are not pregnant, and you have not used CBD products in the past two weeks.

Height, Weight, Body Composition: We will ask you to then remove your shoes so that we can assess your height and weight. We will then ask you to lay flat on their back on a cushioned table so that we can assess your body composition. This requires the investigators to place two sticky pads (electrodes) on your hand and foot (matching sides). The assessment takes less than a minute and only requires you to lay still. You can see the general positioning in the image to the right.

Blood Draw
We will draw two small tubes of blood (4 mL = 0.25 tablespoon, each) by putting a needle into a vein in your arm. This is the standard method used to obtain blood for tests. We will repeat the blood draw fifteen times over the course of this study (five weeks).

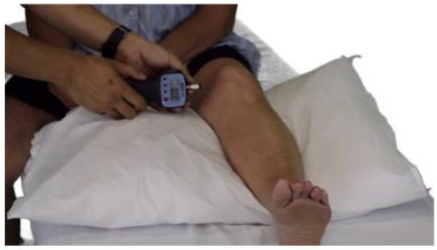
Resistance Training The load will be set at 60% of your body weight. You will complete four sets of back squats with 60% of your body weight on the bar. The first set will be stopped once you reach fatigue (either failing to keep up with the metronome or your technique fails). The second set will follow the same protocol. Sets three and four will follow the same metronome, but you will complete the same number of repetitions as you did in set two.

Muscle Function We will ask you to complete two muscle function tests, both measuring your lower extremity power. The first will be three attempts at vertical jump. You will stand on platforms embedded in the floor (one foot on each platform) with your hands on your hips. When commanded, you will jump as high off the floor as you can, landing safely on both feet and maintaining your balance. You will get at least one minute rest between attempts.

The second test is looking at your movement velocity. We will use the same back squat equipment and 60% of your body weight. When instructed, you will perform one back squat as quickly as you can safely do it while maintaining form and balance. A device will be attached to the bar, measuring the velocity you move. You can see the device pictured below.

Muscle Soreness and Recovery We do anticipate some soreness in the active muscles in the days following the resistance training. We will ask you to make a vertical mark on a visual analog scale (VAS), like the one below, demonstrating how sore you are feeling. Additionally, you will be asked to gauge your subjective recovery and exertion throughout all days of testing.

Next, we will evaluate your pain pressure threshold. We will take a device, as pictured to the right, and gently and gradually apply pressure to the middle of your muscle until you say "stop" → when you feel the first instance of slight uncomfortable pain. We will rotate between your legs' muscles and then repeat the measurements three times in each site to make sure we are accurate. We will also mark each muscle's measurement location with a permanent marker so repeated measurements are the same. You will have this test done each time you visit the lab.



Schedule	Day			
Week 1	**Trial 0**	**Trial 24**	**Trial 48**	**Trial 72**
Visit 1 - Informed consent - Anthropometrics - Familiarization with study techniques - Discuss nutrition guidelines - Give study capsules.	- CBD supplementation 2 hours prior to arrival. - Perceived Muscle Soreness (VAS) - Blood draw - Muscle Function (vertical jump and bar velocity) - Pain pressure threshold (PPT) - Perceptual Recovery - Back squat intervention - Perceived Muscle Soreness - Pain pressure threshold (PPT) - Given capsules for consumption 8 hours later.	Same time of day - Blood draw - Muscle soreness (VAS & PPT) - Perceptual recovery scale - Muscle function - Randomized cocktail immediately & after 8 hours	Same time of day - Blood draw - Muscle soreness (VAS & PPT) - Perceptual recovery scale - Muscle function - Randomized cocktail immediately & after 8 hours	Same time of day - Blood draw - Muscle soreness (VAS & PPT) - Perceptual recovery scale - Muscle function
Seven-day washout period				
Week 2	- Repeat methods from week 1			
Seven-day washout period				
Week 3	- Repeat methods from week 1			
Note: "Weeks" in the table above denotes the actual time spent in the study and not the washout period.				

3. **Discomfort and Risks:** The risks of having blood drawn from your arm include some pain when the needle goes in and a small risk of bruising and/or infection at that site. Some people get lightheaded, nauseous, or faint. You are less likely to have these problems if you drink at least 2 glasses of water and have a snack before the blood draw. The American Red Cross recommends that you do not donate more than 1 pint (32 tablespoons) of blood within a 2-month period – this study requires about 6.75 tablespoons. Tell the study team if you have recently had your blood drawn for any reason.
There are minimal risks associated with the muscle function tests aside from muscle discomfort due to soreness from exercise. The vertical jump is a maximal effort test, so it is possible that the participant may lose their balance when landing on the floor. Participants will be advised to jump as high as they can safely maintain their balance upon landing. We also anticipate very minimal risks associated with bar velocity assessments. However, you will be asked to move the bar as fast as you safely can, so there is always risk of soft tissue injury when lifting weights. We are attempting to lower this risk by having you squat with only 60% of your body weight, which is likely a warmup load for those who regularly train.

There are no anticipated risks to marking perceived soreness on a visual analog scale. Participants may experience discomfort to slight pain with the pain pressure threshold testing. The testing involves applying gradual pressure to targeted muscles that may already be sore due to exercise. The investigator will always communicate with the participant to ensure their comfort is maintained or to stop the test if it becomes too uncomfortable. It is also possible that the location of testing becomes bruised due to the repeated pressure applied to the area. To minimize risks, the investigator will be trained by a licensed physical therapist and will always use the appropriate technique.

Feelings of fatigue or soreness during or after the exercise is anticipated within the first few days if the participant is unaccustomed to the style of exercise. While it is unlikely, there is potential for a musculoskeletal injury because of exercise. Though the risk of injury is present anytime we engage in activity, we anticipate the risk for injury to be low.

Eccentric emphasized exercise does induce more muscle disruption and impairs function more than other types of exercise. Clinical symptoms of this exercise induced muscle disruption often comes in the form of delayed-onset of muscle soreness (stiffness, swelling, loss of force generating capacity, discomfort, pain). Most symptoms of this soreness disappear after a few days. There are currently no anticipated risks associated with CBD supplementation.

4. **Benefits:** The participant will benefit from participating in this study by getting firsthand experience in exercise related research. Participants will experience the benefits of CBD oil on days it is provided (e.g., stress reduction, antioxidants, improved sleep). The cost of participation if volunteers were to purchase the CBD themselves would be about $290. Participants will be compensated for their time at the end of the study equaling $20 per week of study engagement (totaling $60).

5. **Confidentiality:** All information will be de-identified (number instead of name) to maintain confidentiality. The participant's name will only appear on consent/assent document(s). All data collected will be saved on a password-protected WKU computer. Records will be viewed, stored, and maintained in private, secure files only accessible by the P.I. and advising faculty for a minimum of three years following the study. We cannot guarantee that the participant will not be seen performing the research tasks that occur at the data collection site, but they will be performed in a minimally windowed room.

6. **Refusal/Withdrawal:** Refusal to participate in this study will have no effect on any future services you may be entitled to from Western Kentucky University. Anyone who agrees to participate in this study is free to withdraw from the study at any time with no penalty.

You understand also that it is not possible to identify all potential risks in an experimental procedure, and you believe that reasonable safeguards have been taken to minimize both the known and potential but unknown risks. If a medical emergency does occur, you understand that you are responsible for any costs incurred, including but not limited to the services of Emergency Medical Technicians, emergency room care, hospitalization, etc. We strongly encourage you to ensure that you have adequate health insurance coverage or other means of satisfying any costs for which you will be liable.

_____ _____
Signature of Participant Date

_____ _____
Witness Date

- I agree to the audio/video recording of the research. Any recordings will be used for research purposes only ***(Initial here)*** _____

THE DATED APPROVAL ON THIS CONSENT FORM INDICATES THAT
THIS PROJECT HAS BEEN REVIEWED AND APPROVED BY
THE WESTERN KENTUCKY UNIVERSITY INSTITUTIONAL REVIEW BOARD
Robin Pyles, Human Protections Administrator
TELEPHONE: (270) 745-3360

WKU IRB# 22-229
Approved: 9/27/2023
End Date: 9/27/2024
EXPEDITED
Original: 9/27/2023

Appendix B

2023 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 Global Physical Activity Guidelines for your age (https://www.who.int/publications/i/item/9789240015128).
- 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 center may retain a copy of this form for its 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.

 1 / 4
01-11-2022

2023 PAR-Q+

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 currently 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 ☐

2023 PAR-Q+

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.

2023 PAR-Q+

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+
Warburton DER, Jamnik VK, Bredin SSD, and Gledhill N on behalf of the PAR-Q+ Collaboration. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). Health & Fitness Journal of Canada 4(2):3-23, 2011.

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.

Appendix C

What to Eat during the CBD and Resistance Training Study

While in this study, there is no special diet, but all participants are recommended to follow a healthy diet, so use MyPlate to guide you on what to eat. MyPlate is a great visual for healthy eating. When deciding what to eat or drink, choose options that are full of nutrients and limited in added sugars, saturated fat, and sodium. Below are dietary recommendations during this study:

Eat before taking the CBD capsules

Based on previous studies, CBD oil is better absorbed with food. Thus, be sure to eat a meal or snack at least 30 minutes before taking the CBD capsules.

Choose a variety of fruits and vegetables

Use fruits and vegetables in meals or snacks during this study and try different colors of fruit and vegetables. At a minimum, eat at least 2 cups of fruit and 2.5 cups of vegetables daily (having more is even better).

Include whole grains

Fuel your body with nutrient-packed whole grain foods. Make at least half your grains whole grains, such as whole wheat bread, cereal, and, yes, even popcorn!

Enjoy a variety of protein foods

Choose lean or low-fat cuts of meat, skinless chicken/turkey, or seafood. Plant-based foods such as beans, peas, and lentils are good choices as well as protein bars and shakes.

Don't forget dairy

Include foods like fat-free and low-fat milk, yogurt, or calcium-fortified non-dairy beverages like soy or oat milk. Aim to consume three servings of dairy or dairy-substitutes each day while in this study.

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Name: Pacheco Figueroa, Andres Guillermo

Email (to receive future readership statistics): andres.pacheco969@topper.wku.edu

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Title: CANNABIDIOL (CBD) AND RESISTANCE TRAINING: DOES CBD ATTENUATE ACUTE PAIN?

Keywords (3-5 keywords not included in the title that uniquely describe content): Cannabidiol, pain, DOMS, exercise-induced hypoalgesia

Committee Chair: Dr. Whitley Stone

Additional Committee Members: Dr. Danilo Tolusso Dr. Whitley Stone

Select 3-5 TopSCHOLAR® disciplines for indexing your research topic in TopSCHOLAR®: Sport Science Rehabilitation and Therapy Medicine and Health Sciences