THE EFFECT OF WHITE WILLOW BARK ON

DELAYED ONSET MUSCLE SORENESS

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Abstract: Delayed onset muscle soreness (DOMS) is discomfort that occurs within 8-24hrs following an unaccustomed or high-intensity bout of physical activity that peaks within 24-27hrs and slowly resolves on its own. A popular treatment in alleviating the pain associated with DOMS is the consumption of NSAIDs such as aspirin which increases the risk of gastrointestinal (GI) injury upset. White willow bark (WWB) is a nutritional supplement that is believed to have anti-inflammatory and analgesic properties like aspirin but without the risk of GI adverse effects. The purpose of this investigation is to determine the effectiveness of WWB on alleviating the symptoms of DOMS following exercise. Twenty-five individuals volunteered to participate and were randomly assigned to take WWB (798mg salicin) or placebo for 5 days following a lower body resistance training session which consisted of 5X10 lunges at 40% body weight (BW) and 3Xfatigue leg press at 75%BW. Test procedures included Visual Analog Scale (VAS), mid-thigh circumference, pressure pain threshold, vertical jump height, ground-contact time, peak power, and peak velocity. VAS was measured pre, days1-5 of the supplementation period and day 6 (post). All other variables were measured at pre, immediate, day 3(72hrs), and day 6 (post). Twelve two-way repeated measure ANOVAs were utilized in this investigation. No condition X time interaction was observed ($p > 0.05$) for any variable. However, VAS scores were lower in the WWB compared to the placebo for all time frames. There was a significant main effect of time for VAS scores indicating muscle soreness for hamstrings ($p < 0.001$), gluteal ($p < 0.001$), gastrocnemius ($p < 0.001$) and quadriceps ($p < 0.001$). In addition, there was a significant main effect of time for right mid-thigh pressure pain threshold ($p = 0.02$), mid-right ($p < 0.001$) and mid-left ($p < 0.001$) thigh circumference, jump height ($p < 0.001$), ground contact time ($p < 0.001$), peak power ($p < 0.001$), and peak velocity ($p < 0.001$). These findings conclude WWB may reduce subjective feelings of muscle soreness. However, the ability of WWB to maintain athletic performance following DOMS remains inconclusive.

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CHAPTER I

INTRODUCTION

1.1 Introduction

Delayed onset muscle soreness (DOMS) is defined as pain or discomfort that occurs after an unaccustomed or high-intensity bout of physical activity (Cheung et al., 2003). Individuals of all fitness levels (athletes to novice) can experience DOMS following exercise. Clinically, DOMS is considered as a type 1 muscle strain (Safran et al., 1989). Following an extensive training session, DOMS will typically occur within 8-24 hours, peak within 24-72 hours following exercise and slowly resolves on its own within 5-7 days (Manimmanakorn et al., 2016; Ranchordas et al., 2020). The duration for healing is dependent on the severity of the muscle damage and the fitness level of the individual (Cheung et al., 2003; Smith, 1992). Eccentric exercise is well documented as the culprit of DOMS (Proske & Morgan, 2001). An eccentric muscle contraction occurs when the muscle is forcibly lengthened while actively developing tension (Davis et al., 2007; Proske & Morgan, 2001). Any exercise that contains an eccentric component (plyometric exercise, squatting, jumping, downhill running, and the lowering phase of resistance training) will produce greater amounts of muscle fiber damage, inflammation, DOMS, and muscle function deficits (Davis et al., 2007).

The underlying cause of DOMS is not fully understood. Most researchers agree that DOMS is caused by muscle damage (sarcomere disruption) and inflammation (Amalraj, Divya, & Gopi, 2020; Hoseinzadeh, Daryanoosh, Baghdasar, & Alizadeh, 2015) (Figure 1). During eccentric exercise, the sarcomeres become overstretched and following exercise fail to return to their resting length (Brooks et al., 2005). The overstretched sarcomeres allow calcium to accumulate into the injured portion of the muscle (Cheung, Hume, & Maxwell, 2003;Maclntosh et al., 2006). The influx of calcium initiates a surge of signaling that activates both proteases and phospholipases resulting in the production of both prostaglandins and leukotrienes (Cheung, Hume, & Maxwell, 2003;Maclntosh et al., 2006). The leukotrienes increase vascular permeability allowing fluids and intracellular components to enter the cells and neutrophils to invade the area of muscle damage (Maclntosh et al., 2006). The fluids and intracellular components attract macrophages to the injured area (Maclntosh et al., 2006). The invasion of macrophages stimulates free radicals, proinflammatory cytokines (IL-6 and IL-1), and tumor necrosis factor (TNF) production that enhance muscle injury and the chemical stimulation of type II and IV muscle afferent pain receptors resulting in DOMS (Connolly, Sayers, & McHugh, 2003; Maclntosh, Gardiner, & McComas, 2006). The most popular pathway that is proposed to result in DOMS involves the arachidonic acid pathway. Following muscle injury, arachidonic acid is released from the damaged cellular membranes (Maroon, Bost, Borden, Lorenz, & Ross, 2006). Once released, arachidonic acid is quickly transformed into prostaglandins (PGE_2) and thromboxane through the enzyme cyclooxygenase (COX-1 or COX-2) (Maroon, Bost, Borden, Lorenz, & Ross, 2006). COX-1 is a constitutive enzyme that protects the gastrointestinal lining and aids in platelet aggregation (Maroon, Bost, Borden, Lorenz, & Ross, 2006). In comparison, COX-2 is only activated during muscle damage and aids in the production of inflammation and stimulation of type II and IV pain receptors (Maroon, Bost, Borden, Lorenz, & Ross, 2006).

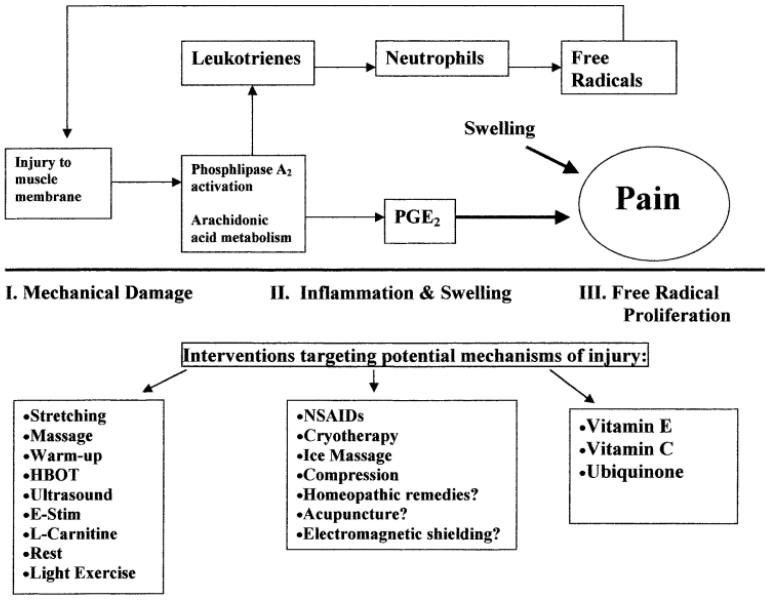

Figure 1- Schematic showing the possible sequence of injury leading to DOMS and Treatment. COX-2, cycloxygenase; PGE_2; prostaglandin E_2 . Adapted from "The Treatment and Prevention of Delayed Onset Muscle Soreness," by Connolly, D.A.J., Sayers, P., & McHugh, M.P. 2003. *Journal of Strength and conditioning, 17*(1), p. 198. Copyright 2003 by National Strength and Conditioning Association.

The sensation of pain can deter an individual from adhering to an exercise program, interfere with activities of daily living, and decrease athletic performance (Ranchordas et al., 2020). Since the mechanism that results in DOMS is not agreed upon, there are many different treatment strategies used in hopes of alleviating pain and maintaining athletic performance. Some techniques used to decrease DOMS include massage (Andersen et al., 2013; Farr et al., 2002; Mancinelli et al., 2006; Zainuddin et al., 2005), heat therapy (Petrofsky, 2013; Petrofsky et al., 2017; Symons et al., 2004) hydrotherapy (Bailey et al., 2007; Sellwood et al., 2005; Vaile et al., 2008), and non-steroidal anti-inflammatory drugs (NSAIDs) (Barlas et al., 2000; Hasson et al., 1993; Meamarbashi & Rajabi, 2015; Riasati et al., 2010; Stone et al., 2002; Tokmakidis et al., 2003). The results of the studies examining different strategies to alleviate DOMS and maintain muscle function following an exhaustive bout of eccentric exercise are mixed. A possible reason for the inconclusive results is a lack of understanding of the exact mechanism responsible for DOMS and the treatment strategy for DOMS may vary between individuals (Hart et al., 2005).

The consumption of NSAIDs or analgesics is the most popular method to treat post exercise pain and soreness (Brewer et al., 2014). Many studies have been conducted to discover the effects of various NSAIDs such as aspirin (Riasati et al., 2010) ibuprofen (Hasson et al., 1993; Stone et al., 2002; Tokmakidis et al., 2003) and indomethacin (Meamarbashi & Rajabi, 2015) and analgesics such as paracetamol (Barlas et al., 2000) on the parameters of DOMS following exercise. Some studies show that NSAIDs decrease DOMS (Riasati et al, 2010; Hasson et al., 1993; Tokmakidis et al., 2003) while other's (Barlas et al., 2000; Meamarbashi & Rajabi, 2015; Stone et al., 2002) concluded that NSAIDs have no effect of DOMS. A survey examining the prevalence of NSAIDs and non-narcotic analgesics use in the United States found that approximately 14% of adults use non-narcotic analgesics daily for pain relief from musculoskeletal injuries and other aliments (Paulose-Ram et al., 2005). Specifically examining colligate athletes, the prevalence of NSAIDs or other non-narcotic analgesics ranges from 17-83% (Brewer et al., 2014). The most common medications used to treat musculoskeletal pain and soreness is acetaminophen, aspirin, and ibuprofen (Brewer et al., 2014). Remarkably, individuals who use NSAIDs or analgesics daily are not bothered by the potential side effects of taking the medication compared to those who take either medication on an acute basis (Wilcox et al., 2005). The use of NSAIDs poses a risk of experiencing adverse effects with a higher risk in those who chronically use NSAIDs. The potential adverse effects associated with NSAIDs include gastrointestinal injuries, gastrointestinal upset, increased risk of blood clots, stroke and liver and kidney injury.

Due to the potential side effects, there has been extensive research done on potentially using nutritional supplements in the alleviation of DOMS and other musculoskeletal issues. It is theorized that nutritional supplements have similar anti-inflammatory properties of NSAIDs without the risk of adverse effects and may be an alternative to NSAIDs in controlling inflammation and oxidative stress following exercise (Nakhostin-Roohi, Moradlou, Hamidabad,

& Ghanivand, 2016). The supplements that may be an alternative to NSAIDs include curcumin, ginger, ginseng, protease, green tea extract and pomegranate. Like the other techniques (i.e., massage, hydrotherapy, heat, and stretching) used to treat DOMS, the results from the numerous studies examining the above-mentioned supplements are mixed. One of the main reasons of the disparity is due the absences of a uniform recommended dosage and duration for the consumption of the supplements for maximal anti-inflammatory and analgesic effects.

1.2 Purpose of Study

Previous research has examined the effects of nutritional supplements such as curcumin, ginger, ginseng, protease, green tea extract, and pomegranate on their ability to alleviate delayed onset muscle soreness and maintaining athletic performance. To the best of our knowledge, no studies to date, have examined the potential of the nutritional supplement white willow bark (WWB) as an alternative to NSAIDs or analgesics to decrease pain and inflammation associated with muscle damage. Therefore, the purpose of this study is to investigate the effectiveness of WWB on alleviating the symptoms of DOMS following exercise.

1.3 Specific Aims

1. The first aim was to investigate if WWB has any effect on the parameters of DOMS (perceived pain/soreness and thigh swelling) compared to placebo following an exhaustive lower body resistance training session.

2. The second aim was to determine if WWB could maintain athletic performance (vertical jump height) following an exhaustive lower body resistance training session.

1.4 Research Questions

1. Does WWB decrease DOMS compared to placebo following an exhaustive lower body resistance training session?

2. Does WWB maintain sport performance (vertical jump height) compared to placebo following an exhaustive lower body resistance training session?

1.5 Hypothesis

1. H_O: There will be no difference between the placebo and WWB in parameters of DOMS following a damaging lower body resistance training session.

   H_A: There will be a significant difference between the placebo and WWB in parameters of DOMS following a damaging lower body resistance training session.

2. H_O: No difference between the placebo and WWB in athletic performance (vertical jump height) following a damaging lower body resistance training session.

   H_A: There will be a significant difference between the placebo and WWB in sport performance (vertical jump height) following a damaging lower body resistance training session.

1.6 Significance of Study

In the United States in 2000, 111 million NSAID prescriptions were written by physicians for the treatment of musculoskeletal pain (Laine, 2001). A recent study has shown that 14 million Americans use NSAIDs for minor muscle aches and another 36 million use NSAIDs for the treatment of pain (Wilcox et al., 2005). Surprisingly, many of the long-term users are not concerned with the adverse effects that are common with the consumption of NSAIDs. In addition, each year approximately 100,000 individuals are hospitalized for gastrointestinal complications resulting from the use of NSAIDs with a cost ranging from $1,800-8,500 per hospital stay (Fine, 2013). It is projected that the use of NSAIDs is going to continue to rise in the United States because of an increase in life expectancy (Fine, 2013). Americans are living longer today due to the advancement in health care. With aging comes the increase risk of chronic pain and other conditions that require either an acute or chronic use of NSAIDs for treatment. Consequently, the increase use of NSAIDs is correlated with an increased risk of adverse effects. Therefore, it is imperative to identify alternatives to aspirin and other NSAIDs that offer the similar analgesic and anti-inflammatory effects without the risk of adverse effects. One of those potential alternatives to aspirin and other NSAIDs is WWB.

To date, literature examining the effects of WWB has been done only on a clinical population, such as those with osteoarthritis, chronic low back pain, and rheumatoid arthritis. Studies examining the effects of willow bark on perceive pain and inflammation have been sparse with results showing a potential for willow bark as a safer or tolerable alternative to NSAIDs. The current study has the potential to discover an alternative to NSAIDs or analgesics in the management of DOMS and other minor musculoskeletal injuries. If successful, WWB may serve as an alternative to NSAIDs in those individuals who take NSAIDs for the occasional muscle aches or pains and for those who cannot tolerate NSAIDs.

1.*7 Delimitations*

1. Participants were limited to 18-35 years of age.
2. This investigation required the recruitment of approximately 30 males and females to complete the study.
3. All participants were required to be healthy and free from any sign or symptom of disease, and be without any musculoskeletal injury, previous surgery within the last 6 months (i.e., hip, low back, knee, and ankle), without a diagnosis of all types of arthritis (i.e., osteoarthritis, gout, rheumatoid arthritis etc.) or have chronic low back pain.
4. This investigation required the participants to not be participating in a low body resistance program on a regular basics (at least 3 days a week for the last 3 months).
5. This investigation required the participants to refrain from participating in any exercise or physical activity program involving the lower body during the duration of the study.
6. The investigation required that the participants refrain from taking any NSAIDs, analgesics, corticosteroids, or any type of nutritional aid that could interfere with the therapeutic actions of WWB.
7. All participants were not taking medication that may interfere with WWB (i.e., anticoagulants, beta blockers, diuretic, methotrexate, or phenytoin).
8. The investigation required that all participants not have a known allergy or sensitivity to salicylates such as aspirin.

1.8 Limitations

1. Participants were recruited through responding to a classroom visit, recorded Zoom video, poster flyer, and word of mouth. Therefore, this was a convenience sample.

2. The investigators had no control on the participants' level of motivation during each visit which may have influenced their ability or level of effort when performing the vertical jump.
3. The investigators could not control for any influence such as activity, diet, timing of WWB intake, and/or sleep outside of the visits, which may have impacted the results of the study.
4. The investigators could not control when the participants filled out their visual analog scale each morning to rate their muscle soreness/discomfort which may have impacted the results of the study.

1.9 Assumptions

1. The participants were truthful when answering the questions on the health history and exercise questionnaire

2. The participants were not participating lower body resistance program on a regular basis that included: leg extension, squats, leg press, lunges, dead-lift, or hamstring curls.

3. The participants were taking the WWB or placebo as directed (2 tablets 3 times daily with food) during the supplementation period.

4. The participants were truthful and filled out their visual analog scale to rate their pain and discomfort within 30 minutes of waking each morning.

5. The fatiguing protocol used in the investigation was effective in inducing acute muscle damage resulting in DOMS.

6. The participants did not take any NSAIDs or other analgesic medication (prescription, over-the counter or nutritional aids) and did not participant in any technique (i.ec.,

massage, heat, topical creams, stretching, exercise, or hydrotherapy) that had the potential to decrease DOMS for the duration of the study.

7. The technology and equipment utilized for data collection functioned as intended by the manufacturers.

8. No error occurred during the data collection, data analysis, data entry, and/or statistical processing.

CHAPTER II

REVIEW OF LITERATURE

The aim of this review of literature is to examine aspirin and the mechanism it acts upon to decrease pain and inflammation. In addition, the adverse effects of aspirin are examined justifying the need to find more natural remedies to alleviate pain and inflammation. The history of willow bark and the proposed mechanism that willow bark acts upon to decrease pain will be reviewed. In addition, studies investigating the efficacy of willow bark in the treatment of musculoskeletal disorders are examined.

2.1 Aspirin

2.1.1 Recommended Dosage of Aspirin

Salicylates such as aspirin are one of the oldest and most common drugs consumed by man because of its antipyretic, anti-inflammatory, and analgesic effects. Approximately 100,000 Americans over the age of 40 consume aspirin everyday (Kim & Beckles, 2004). Aspirin has many beneficial uses such as decreasing the risk of heart attacks in those with cardiovascular disease and preventing transient-ischemic attacks and stroke. Therefore, many Americans consume aspirin for the primary of secondary prevention of cardiovascular disease (Ittaman et al., 2014). In addition, aspirin has been shown to decrease the risk of developing colon and rectum cancer (Ugurlucan et al., 2012). The dose of aspirin consumed often dictates whether an individual receives a cardioprotective or an analgesic effect. Typically, a low dose ranging from 75-325mg per day is associated with a cardioprotective effect used in the primary and secondary prevention of cardiovascular disease (Sostres & Lanas, 2011). A dose greater than 325mg is often recommended for pain relief (Sostres & Lanas, 2011).

2.1.2 Proposed Mechanism for Anti-inflammatory and Analgesic Effects

It is theorized that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) acts upon the arachidonic acid pathway to slow the inflammation cascade (Figure 2). Aspirin and NSAIDs decrease pain and inflammation by the inhibition of the cyclo-oxygenase (COX) enzymes which catalyze the conversion of arachidonic acid (AA) to proinflammatory prostaglandin E2 (Vane & Botting, 1998). There are two main forms of the cyclo-oxygenase enzyme, COX-1 and CO-2. COX-1 is a constitutive enzyme that protects the gastrointestinal lining and aids in platelet aggregation (Maroon et al., 2006). In comparison, COX-2 is only

activated following muscle damage and facilitates the production of inflammation and stimulation of type II and IV pain receptors (Maroon et al., 2006). Both COX isoforms catalyze the conversion of arachidonic acid to prostaglandins (Lanier, 2003). Aspirin preferentially inhibits COX-1 over COX-2 (Lanier, 2003; Sostres & Lanas, 2011). Unlike other NSAIDS, aspirin is also believed to inhibit the synthesis of prostaglandin E2 by the irreversible acetylation of COX-1. Prostaglandin E2 serves as key mediator of acute inflammation. (Vane & Botting, 1998). Prostaglandin E2 and prostacyclin are vasodilators that act in sync with bradykinin and histamine to produce swelling and pain following injury (Vane & Botting, 1998; Wolfe et al., 1999).

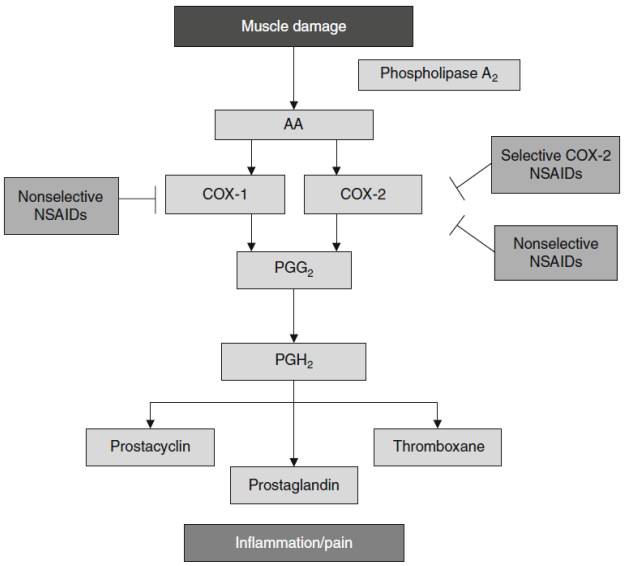

Figure 2- COX inflammatory pathway from muscle damage and the proposed mechanisms of aspirin and NSAID action on the process. Adapted from "The Use of Nonsteroidal Anti-Inflammatory Drugs for Exercise- Induced Muscle Damage," by B.J Schoenfeld, 2012, *Sports Medicine*, 42(12), p. 1091. Copyright 2012 by Springer International Publishing AG.

2.1.3 Adverse Effects Associated with Aspirin

The use of aspirin for most of its therapeutic effects does not come without risk. One of the most common adverse effects in those that consume aspirin is gastrointestinal upset or injury (Cryer, 2010; Sostres & Lanas, 2011). Unknown to the consumer, each time they take an aspirin

they are subjected to small breaks in the epithelial lining which resolves quickly own its own (Silen & Ito, 1985). If the damage is severe enough to penetrate the mucosa repair is typically achieved within 1-3 days. More serious injuries such as gastrointestinal lesions or ulcers can take weeks up to months to heal (Silen & Ito, 1985). Within in the general population, those who consume aspirin on a regular basics, have a two-fold increase in developing a gastrointestinal bleed (Cryer, 2010; Weil et al., 1995). In addition, 15% of individuals who consume aspirin with a history of bleeding stomach ulcers will have a recurrent bleed within one year of the initial event (Cryer, 2010; Weil et al., 1995).

Gastrointestinal injury can occur through two different mechanisms, topical mucosal injury, or systematic effects (Cryer, 2010). Topical mucosal injury is due to local effects within the gastrointestinal mucosa. When the gastroduodenal mucosa comes into direct contact with aspirin it can result in damage by disrupting the gastric epithelial cell barrier (Tomisato et al., 2004). Surprisingly, this can occur within minutes of expose to acetylated salicylate acid (aspirin) (Tomisato et al., 2004). Systemic effects leading to gastrointestinal injury is mediated by the inhibition of COX-1. The blocking of COX-1 depletes gastrointestinal mucosal prostaglandins inhibiting basal gastric acid and stimulates gastric acid secretion (Jaramillo et al., 1989). The systematic effects are the main mechanism that leads to damage in the upper gastrointestinal mucosa (Darling et al., 2004). The adverse effects of aspirin are not limited to the gastrointestinal system. The use of aspirin and other NSAIDs can lead to both liver and renal injury in addition to the accelerated development of heart failure in those who are already at risk (Lanier, 2003; Page & Henry, 2000).

2.2 Willow Bark (Salix aba L.)

2.2.1 History of Willow Bark

Willow bark (*Salix alba* L.) is obtained from the whole or fragmented dried bark of young (2-3 years old) branches or twigs from various species of *Salix* belonging to the *Salicaceae* family (Viltrakyte, 2008). The bark of the willow tree contains no more than 1% total salicin derivatives which is calculated based upon salicin in relation to the dried herb (Viltrakyte, 2008).Worldwide, there are approximately 400 willow species with the Salix species located in the North Temperature and Arctic regions (Lévesque & Lafont, 2000; Saller et al., 2008; Wood, 2015).

Historical records show that willow bark has been used for thousands of years in ancient China, Egypt, Greece, and South Asia to alleviate headaches, fever, pain and in the treatment of numerous other illnesses (Oketch-Rabah et al., 2019). The Sumerians were the first to document the use of willow bark as a prescription for pain on clay tablets approximately 4,000 years ago (Wood, 2015). In 4th Century BC, Hippocrates, the father of medicine, instructed patients to chew the bark from the willow tree or drink the powder extract to relieve fever, pain, and inflammation (Oketch-Rabah et al., 2019). In addition, it is documented that the Babylonians chewed the leaf extract or bark from the willow tree as a remedy for pain, inflammation, and fever (Wood, 2015). The first modern medical documentation of the effect of willow bark occurred in 1763 when a priest named Edward Stone published the medical report in the *Philosophical Transactions of the Royal Society* on the effectiveness of willow bark in decreasing fever (Ugurlucan et al., 2012). Stone proposed that the English white willow bark could yield a treatment to rheumatic diseases and cure malaria. To test his theory, Stone dried out bark from the white willow tree and shifted the bark into a fine powder. Stone took approximately 20g of the powder every four hours and discovered that his fever and accompanying symptoms was eradicated with the treatment with no side effects (Stone, 1776). For the next five years, Stone tested the powdered willow bark extract on participants and concluded that consuming approximately 3.5g of white willow bark extract

(approximately 2% salicylates) was effective in decreasing fever associated with malaria (Stone, 1775; Woods, 2015).

The transition from folk medicine to lucrative medicine occurred in 1827 when the Johann Buchner isolated the pharmacological active ingredient salicin from the bark of the willow tree and in 1829 the French chemist Henri Leroux obtained 30g of salicin from 1.5kg willow bark (Ugurlucan et al., 2012). Following the discovery of salicin, in 1838, an Italian chemist Raffaele Piria split the salicin into a sugar and an aromatic component by creating salicylic acid (Mahdi, 2010). The willow bark era ended in 1860 when the chemists Kolbe and Lautemann discovered how to synthetically produce salicylic acid leading to the mass, commercial production of salicylic acid (Viltrakyte, 2008). During the 19th century, physicians prescribed either salicin or salicylic acid in the treatment of rheumatic fever, gout and as an antipyretic and analgesic drug (Wood, 2015).While effective in treating the forementioned conditions, the typical doses prescribed (8-10g daily) often resulted in gastric irritation and upset (Saller et al., 2008). To offset the adverse effects of synthetically produced salicylic acid, Bayer chemists set out to produce a stable acetylated salicylate which is known worldwide today as Aspirin (Saller et al., 2008).

2.2.2 Willow Bark's Proposed Mechanism of Action

One of the active ingredients in willow bark is salicin. The prodrug salicin is stable in acidic conditions such as the human saliva (Bonaterra et al., 2010). Once ingested, through hydrolysis and β-glucuronidase salicin is converted to saligenin in the stomach and is further broken down to salicylic acid in the liver by the cytochrome P 450 system (Bonaterra et al., 2010). Akao, Yoshino, Kobashi, and Hattorui (2002) conducted a study to compared salicin, saligenin, and salicylic acid in three different experiments. The researchers examined the

absorption of salicin and its derivatives after oral consumption in rats. After oral ingestion, salicylic acid appeared in blood plasma rapidly and was dose dependent. In comparison, when the rats orally ingested salicin, salicylic acid appeared slowly and no saligenin was detected. Interestingly, the researchers found when salicin was administered orally, salicin itself was poorly absorbed in the small intestine and was only absorbed once it ransformed into saligenin. In rats, once salicin is transformed into saligenin by bacteria in the intestine it is quickly transformed into salicylic acid. In rats, low levels of salicylic acid were maintained up to 17 hours. Based on this study, the researchers concluded that salicin appears to be activated gradually in rats. As of date, the absorption of the active ingredient salicin has not been studied in humans. However, it is speculated that in humans, the absorption of salicin is like that of rats.

It is theorized that willow bark and its constitutes have inhibitory actions on the arachidonic acid pathway. More specifically, willow bark may target COX-1 and COX-2, to decrease pain and inflammation like aspirin. Recently, it has been found that many different compounds in addition to salicin exists in willow bark. Therefore, the exact mechanism in which willow barks upon to produce both anti-inflammatory and analgesic effects is not agreed upon. Through mechanism studies done in both in vitro and vivo, willow bark is believed to inhibit lipoxygenase, (Bonaterra et al., 2010; Fiebich & Chrubasik, 2004), inhibit COX-2 (Bonaterra et al., 2010; Fiebich & Chrubasik, 2004), prevent cytokine release (Altinterim, 2013), and have antioxidant effects (Ishikado et al 2013; Khayyal et al 2005) which contributes to its overall pharmacological effects (Ishikado et al., 2013). Many studies have been conducted to determine the effects of willow bark on the various mediators of the inflammatory cascade. For instance, in a vitro study, Bonaterra et al (2010) revealed that the aqueous willow bark extract (STW 33-I) significantly inhibits the pro-inflammatory cytokines, tumor necrosis factor alpha (TNFα), COX-2 and nuclear translocation factor (NFκβ). These results support the assumption that willow bark has an inhibitory effect on the arachidonic acid pathway. Khayyal et al (2005) conducted a in

vivo study to discover willow barks role as an anti-inflammatory agent in rats under two conditions that represented both chronic and acute arthritis. Willow bark extract was compared to the anti-inflammatory doses of both aspirin (non-selective COX inhibitor) and celecoxib (selective COX-2 inhibitor). The authors found that willow bark was just as effective as aspirin in decreasing inflammation and suppressing prostaglandin release and more effective than aspirin in inhibiting COX-2. In addition, willow bark extract displayed superiority over both aspirin and celecoxib in the protection against oxidative stress.

Fiebick and Chrubasik (2004) conducted a study in vitro to discover the effects of willow bark on human monocytes. The effects of the willow bark extract, salicin, and salicylate on selective cytokines (IL-6, and IL-β) and COX-2 mediated PGE_2 release was evaluated against a Rofecoxib (selective COX-2 inhibitor) like compound. Compared to Rofecoxib like compound, significantly more willow bark extract was needed to inhibit the COX-2 mediated PGE_2 while salicin and salicylate acid alone had no effect on inhibiting COX-2 or cytokine release. The results also demonstrated that neither salicin nor salicylate acid influenced COX enzyme activity. Based on this observation, the researchers speculated that willow bark extract influences COX enzyme activity through the inhibition of phospholipase A2 (PLA2) which produces arachidonic acid (the substrate of COX). Lastly, the researchers discovered that the willow bark extract successfully inhibited both the release of cytokines IL-1β and IL-6 while the Rofecoxib like compound had no effect on cytokine release. The results from the aforementioned studies reveal that willow bark appears to target mediators of the arachidonic acid pathway. Surprisingly, it was shown that willow bark processes less than a sixth of the amount of salicin. Therefore, it is logical to assume that the anti-inflammatory effects of willow bark must come from other constituents such as polyphenols, due to the observed superiority in decreasing oxidative stress in the form of free radial scavenging.

2.2.3 Components of Willow Bark

Willow bark extract is accepted as both an analgesic and anti-rheumatic drug (Bonaterra et al., 2010; Vlachojannis et al., 2009). A common belief and misconception is that salicin or its metabolite salicylic acid is responsible for willow barks analgesic and anti-inflammation properties (Altinterim, 2013; Saller et al., 2008).Compared to aspirin, willow bark is shown to contain a low quantity of salicin that is metabolized into salicylic acid in the liver (Altinterim, 2013). In fact, compared to others *salix* species, willow bark has the lower salicin concentration (Schmid et al., 2001). A single dose of willow bark containing 240mg of salicin produces a salicylate concentration equivalent to a low dose aspirin (100mg) (Vlachojannis et al., 2009). At the highest recommended dosage of salicin (240mg), it appears that this would correlate to more of a cardioprotective dose rather than an analgesic dose (Schmid et al., 2001).

Assuming willow bark had 100% bioavailability, a dosage of 240mg salicin would be converted to only 115mg of salicylic acid (Schmid et al., 2001).This amount of salicylic acid is not large enough to produce any analgesic or anti-inflammatory effects (Oketch-Rabah et al., 2019). Peak salicylic acid concentration is observed within two hours after consumption (Schmid et al., 2001). Therefore, it seems logical to assume that the pharmacological activity must come from other sources. The anti-inflammatory and analgesic effect of willow bark may come from other compounds identified in willow bark such as polyphenols, derivatives of salicin, condensed tannins, and other compounds such as p-hydroxybenzoic, vanillic, cinnamic, p-coumaric, ferulic, caffeic acids and other phenolic acids (Altinterim, 2013; Drummond et al., 2013; Freischmidt et al., 2012; Harbourne et al., 2009; Oketch-Rabah et al., 2019).

The most popular belief among researchers is that the anti-inflammatory effects of willow bark is due to high levels of polyphenols (salicylates, flavonoids, proanthocyanidins, and tannins) and the different effects of these compounds on distinct targets (Oketch-Rabah et al., 2019). Several studies (Drummond et al., 2013; Freischmidt et al., 2011) have been done in vitro to bring

clarity on the role that polyphenols play in the anti-inflammatory effects of willow bark. Freischmidt et al (2011) tested the inhibitory effects of aqueous willow bark extract (STW 33-1) at 10μg/ml and 50μg/ml on tumor necrosis factor (TN-α) induced intercellular adhesion molecule-1 (ICAM-1) expression in endothelial cells. ICAM-1 is believed to play a role in the inflammatory process in endothelial cells by initiating the process of atherosclerosis. The results of this in vitro study showed STW 33-1 had a significant dose dependent reduction of ICAM-1 compared to the control. The authors partitioned the aqueous willow bark to determine which polyphenols were responsible for the decrease in inflammation. Through a liquid/liquid partition protocol, it was discovered that the presence of catechol and flavanone aglycone eriodictyol where the only isolated polyphenols to show anti-inflammatory activity. The author's concluded that in vitro, catechol, flavonoids and salicin derivatives contribute to the anti-inflammatory activity of willow bark.

Drummond et al., (2013) examined the effects of the aqueous willow bark extract (STW 33-1), chamomile and meadowsweet and their isolated polyphenolic compounds (salicylic acid, apigenin, and quercetin respectively) on anti-inflammatory activity using IL-Iβ, IL-6 and TNF-α as the biomarkers of inflammation in a macrophage cell model at both high (50μL) and low (10μL) concentrations of the willow bark extract. The results revealed that 7.5g willow bark extract contained 7.74g/L of phenols and that the willow bark extract showed the greatest reduction of inflammatory mediated cytokine activity at both high and low concentrations of the extract. The isolation of the polyphenols revealed that salicylic acid induced the lowest anti-inflammatory effects compared to apigenin and quercetin. The researchers concluded that polyphenols contributed to the anti-inflammatory and antioxidant properties of willow bark extract. The results from the aforementioned studies show, contrary to popular belief, willow bark extract is not a natural form of aspirin. The extend in which salicin and salicin derivates contribute to the anti-inflammatory and analgesic effects of willow bark appear to be minimal compared to polyphenols, flavonoids, and other compounds.

2.2.4 Recommended Dosage and Regulation

To date, there is no uniform recommended dosage of willow bark extract. Currently, guidelines suggest an allowance ranging from 7.5 to 900mg of extract per day with no more than 240mg of salicin (Oketch-Rabah et al., 2019). There are many different willow bark products on the market and there is disparity in the recommended dosage with doses ranging from less than 100mg extract per day to over 800mg extract per day (Oketch-Rabah et al., 2019). The European Medicine Agency (EMA) recommends a daily dose of 393-1572mg extract corresponding to no more than 240mg salicin consumed for no more than four weeks at a time (European Medicines Agency, 2017).

While the recommended intake is similar in both Europe and the United States, there is a distinct difference in the regulation and the recognition of willow bark extract for its pharmacological properties. For instance, in the United States, willow bark in not recognized by the U.S Food and Drug Administration (FDA), instead it is listed only as an old dietary ingredient in the United Natural Products Alliance (Oketch-Rabah et al., 2019). In Canada, willow bark is recognized as a natural health product. In Europe and Australia, there is more regulation on willow bark. In both countries it is recognized as herbal medicine with established use with scientific data supporting the recommended dosages and uses of the extract (Oketch-Rabah et al., 2019). Currently, where willow bark is marketed as a dietary supplement, there is not a required label with safety guidelines regarding contraindications, pregnant women, or children. Like aspirin, pregnant women and those breastfeeding should avoid the consumption of willow bark due to the lack of literature investigating the effects on this population (Oketch-Rabah et al., 2019). As stated earlier, willow bark contain salicylates, those allergic or sensitive to aspirin and those currenting taking aspirin and other NSAIDs should use caution when taking willow bark (Altinterim, 2013).

2.3 Effectiveness of Willow Bark in Decreasing Pain

2.3.1 Low Back Pain

Low back pain is one of the most common musculoskeletal complaints worldwide (Gouveia et al., 2017) and is the leading cause of disability (Bhatia et al., 2020). Analgesics and NSAIDs are the standard treatment for low back pain with opioids being the most common prescribed medication (Bhatia et al., 2020; Gouveia et al., 2017; Shmagel et al., 2018) It is estimated that 1 in 5 Americans use opioids to treat their back pain (Bhatia et al., 2020; Gouveia et al., 2017; Shmagel et al., 2018). These medications, while effective in treating low back pain, are accompanied with risks such as addiction, gastrointestinal injury, hospitalization and even death. Recently, there has been an influx in research done on the effects of more natural remedies in the treatment of low back pain to decrease the potential adverse effects that are associated with the classic anti-inflammatory and analgesic medications.

The efficacy and tolerability of willow bark has been studied in patients suffering from low back pain. Churbasik et al. (2000) examined the effects of a low dose (120mg) or a high dose (240mg) of salicin or placebo on chronic low back pain. In this randomized placebo controlled study participants took either the low (n =70) or high dose (n =70) willow bark extract or placebo (n =70) for four weeks. During this time, participants were allowed up to 400mg of tramadol daily as a rescue medication. The outcome measures for this investigation were the proportion of participants pain free for at least five days during the last week of the study, the proportion of patients who needed tramadol, and the change in the modified version of the Arhus Low Back Pain Index. Once a week, the researchers called the participants and asked about their level of pain, dose of tramadol consumed and if they had any adverse events that week. The results showed that 21% of participants in the low dose willow bark, 39% participants in the high dose

willow bark, and 6% participants in the placebo group were pain free and not taking tramadol at the end of the study. In addition, significantly ($p < 0.05$) more participants in the high dose willow bark group saw pain relief after one week of treatment. In the low dose willow bark group, participants experienced significantly ($p < 0.05$) more pain relief after the second week of treatment compared to the placebo group. Overall, significantly ($p < 0.05$) more participants needed tramadol in the placebo group compared to both willow bark extract groups. In this study, the researchers observed a dose-dependent effect regarding pain relief in participants who suffer from low back pain. The researchers concluded that willow bark may be an effective alternative to NSAIDs in those with back pain and cannot tolerate NSAIDs.

Chrubasik et al. (2001a) conducted a four-week, open, non-randomized investigation on the economic effect of willow bark extract (Assalix) on the treatment of acute exacerbations of chronic non-specific back pain. There were 439 participants that completed the study with group one (n=115) receiving two capsules of Assalix per day (approximately 120mg salicin per day), group two (n = 112) received four capsules of Assalix per day (approximately 240 mg salicin per day) and group three (n = 224) received other conventional treatments that their doctors deemed appropriate. All groups were able to take part in other conventional treatments (nerve block, acupuncture, or transcutaneous electrical nerve stimulation) and could consume NSAIDs as needed. The modified Arhus Index (Chrubasik et al., 1996) to assess pain, disability, and physical impairment and the Total Pain Index 9 Chrubasik et al. (2000) to measure pain while sitting, lying, upright, moving, and at night were measured at the beginning and end of the study. In addition, after the first and second week of treatment, the patients were contacted by the researcher to evaluate their overall well-being, occurrence of adverse effects, and to document any changes in the treatment of their back pain. At the end of the study, 16% of participants in group one, 30% in group two and 17% in group three were pain free. A dose dependent effect on the patients belief of treatment success, feelings of well-being and the proportions of patients who

did not need additional treatment was observed. It was found that 73% of participants in group two (240mg salicin) believed the treatment was successful while group one (120mg salicin) and placebo had similar responses to treatment success (63% and 64% respectively). In patients receiving the high dose of willow bark extract, only 30% needed additional treatments compared to 45% in the low dose extract group. In addition, less than 25% of the patients receiving Assalx used additional NSAIDs during the four-week treatment period. Regarding cost effectiveness, those receiving Assalx spent 14-50% less money during the four-week period on treatment compared to group three who receive traditional care for low back pain without Asslax. Based on the results this study, the authors concluded the cost of treating low back pain could be lowered by including willow bark extract into the treatment regimen. Due to the absence of randomization in the study and that patients could continue with other treatment regimens, any effectiveness of Asslax in decreasing low back pain cannot be confidently contributed to Asslax alone.

A third study by Chrubasik and colleagues (2001b) compared the effects of willow bark extract (Assalix) and Rofecoxib (selective COX-2 inhibitor) on low back pain in an open randomized study with 228 participants with non-specific low back pain lasting at least six months taking part the four-week study. Participants were randomly placed in the Assalix group (n = 114) where they consumed four capsules per day which was equivalent to 240mg of salicin or the Rofecoxib group (n= 114) who consumed a single 12.5mg tablet daily. The participants were instructed to continue with their other medications, NSAIDs and other conventional treatments (massage, physical therapy etc.). The outcome measurements, perceived pain on a VAS, the Modified Arhus Index(Chrubasik et al., 1996), and the Total Pain Index (Chrubasik et., al 2000) were measured at baseline and once again at the end of the study. The results showed that both groups had similar treatment effects. Combining the groups together, the pain component on the Arhus Index improved by 30%, Total Pain Index improved 35% and the modified Arhus Index improved by 20%. In each group, 20 participants were completely pain

free following the four-week treatment period. Regardless of grouping, 21 participants required additional treatment. In the Assaix group, the additional pharmacological treatment for pain relief was equivalent to 120mg Diclofenac and 5mg tramadol over the four weeks. In comparison, the Rofecoxib group on average required less NSAIDs (42mg Diclofenac equivalent) but more tramadol (17mg) over the course of the study. Based on the results of the study, the researchers concluded that Assalix is just as effective as Rofecoxib in treating low back pain.

2.3.2 Arthritic Conditions

Arthritis consists of a variety of conditions such as osteoarthritis, gout, rheumatoid arthritis, or coxarthrosis. Between the years of 2013-2015 in the United States, 54.4 million Americans were diagnosed with arthritis and required treatment (Barbour et al., 2017). The use of NSAIDs is often long-term in the management of symptoms and in treatment of pain (Crofford, 2013). The long-term use of NSAIDs often lead to adverse events that can lead to hospitalization or death. Therefore, scientists and researchers have been searching for a more homeopathic treatment for these conditions and one of the potential alternative treatments is the extract from the willow bark tree.

Biegert, et al (2004) conducted a six-week, three arm, randomized controlled study to compare the efficacy of willow bark to Diclofenac and a placebo. To be eligible to participate, participants had to be diagnosed with osteoarthritis in either the hip or knee and not had corticosteroids or surgery involving the effected joints eight weeks prior to the start of the study. The study consisted of an osteoarthritis and rheumatoid arthritis trial in which 127 outpatients with hip or knee osteoarthritis and 26 outpatients with active rheumatoid arthritis took part in this study. In both trials, a washout period lasting 4-10 days (depending on the half-life of the analgesic or NSAIDs) took place before the start of the study. For the osteoarthritis trail, the

participants were randomly placed in one of the three conditions (willow bark extract, Diclofenac or placebo). The willow bark dosage was two tablets, two times daily for a total of 240mg of salicin per day. The Diclofenac group took two tablets, twice daily resulting in a total of 10mg per day while the placebo took two sugar tablets daily. Each participant took their medication for six weeks, 30 minutes before meals in the morning and afternoon. During the study period, the participants were allowed up to 100mg of aspirin per day if needed for pain and inflammation. The participants were assessed by a physician on day -7, 0, 14 and 42 and the participants completed a questionnaire on day 28 on the efficiency on the medication. Pain was addressed by the Western Ontario McMaster University Osteoarthritis Index (WOMAC), safety of drug (blood and urine samples), and the participants assessment of tolerability on a 100mm visual analog scale (VAS) and a perceived quality of life on short form -36 (SF-36) on day 0 and day 42. After six weeks of treatment, the results showed that all groups had improved. Regarding the WOMAC pain score, the Diclofenac group had a significant ($p < 0.05$) pain reduction (23mm) while the willow bark and placebo had similar improvements in pain (8mm and 5mm respectively). In addition, the Diclofenac group had significant ($p < 0.05$) improvements over the placebo regarding joint stiffness, body pain, physical function, and physical role. Once again, the willow bark extract group had comparable results to that of the placebo in all variables except for physical function. Both the patients and treating physicians agreed that the Diclofenac resulted in strong improvements while the willow bark extract resulted in minimal improvements compared to the placebo.

In the rheumatoid arthritis trail, participants were randomly placed in either the placebo (n = 13) or willow bark extract (n =13) condition. While the dosage of the willow bark extract was the same as the osteoarthritis trial, the participants were allowed no more than 7.5mg of corticosteroids and no more than 100mg of aspirin per day to control pain and inflammation. The same study designed was carried out in this trial as it did for the osteoarthritis trial. The results

from the rheumatoid trial showed that at baseline the willow bark extract group had a more active disease state compared to the placebo. While not statistically significant ($p > 0.05$) after six weeks, willow bark extract decreased pain greater than the placebo (15% and 4% respectively). Secondary outcomes such as number of painful, tender, or swollen joints, disability index, and severity of morning stiffness was not significantly different than placebo. The authors concluded that they found no evidence that willow bark extract exhibits any analgesic or anti-inflammatory effects in those with osteoarthritis or rheumatoid arthritis. Based on the results, it is speculated that the dose of willow back used (240mg salicin) was not large enough to have any success the treatment of osteoarthritis or rheumatoid arthritis.

Saller, Melzer, and Felder (2008) conducted a 6-8 week observational study with a control visit after week three and four on the effectiveness of willow bark extract (Assalix) relieving pain in patients with rheumatic pain in the neck or back. In total, 204 physicians treating 763 patients with rheumatic pain participated in the study. The variables of interest were pain, intensity of pain, impairments of daily activities, and a global assessment of efficacy and tolerability. Pain was assessed on a 0-9 scale and following treatment with Assalix had decreased by 2.81$\pm$ 2.11 points (pre: 5.32$\pm$1.62; post: 2.51$\pm$ 2.04). In fact, 14% of the patients were completely pain free after 30. 01 $\pm$ 18.86 days of treatment. In addition, at the start of treatment only 0.6% of patients stated they had no impairments of daily activities, Remarkably, at the end of the study, 27.4% stated they had not impairment of daily activities. The global assessment revealed that 65.8% of patients believed that the willow bark extract was effective in treating their pain and 62% of the patients continued with Assalix after the completion of the study. The authors discovered a dose-dependent response in terms of pain reduction. A higher dose (3-4 tablets per day) was slightly more effective than the recommended dose of 1-2 tablets per day. While researchers believed that willow bark extract is well tolerated and offers a moderate

analgesic effect, the results should be regarded with caution because there was not a placebo nor a control group.

Schmidt et al (2001) assessed the efficacy of willow bark in a two-week double-blind randomized controlled study in patients with a confirmed diagnosis of knee or hip osteoarthritis. The participants were randomly placed into the placebo or willow bark extract group (two tablets twice a day, corresponding to 240mg salicin per day). Both groups took their medications 30 minutes before meals in both the morning and noon. After a 2-4 day washout with a placebo, the participants were treated with either willow bark extract or placebo. Participants were assessed by a physician on days -4, 0, 7, and 14 of the study. Participants rated their physical function and pain on a 100mm VAS every evening. On days 7 and 14 the participants filled out the WOMAC questionnaire that assessed pain, stiffness, and physical function. Compliance and adverse events were checked with a tablet count and diary entries, respectively. At the end of the two week treatment period, there was a significant difference between the placebo and willow bark extract groups in the WOMAC pain dimension (d= 6.5mm, $p = 0.047$). The WOMAC pain score was 14% lower in the willow bark extract group in comparison to the placebo group which had a 2% increase in pain. Physical function and stiffness improved more in the willow bark extract group, but the change was not statistically significant ($p > 0.05$) compared to the placebo group. Lastly, there was a significant improvement in disease state in the willow bark extract group reported by both physicians ($p = 0.0073$) and participants ($p = .0002$).

Beer and Wegener (2008) conducted an open observational study on adults from the ages of 50-75 years old with coxarthrosis with hip pain or gonarthosis with knee pain. The participants had to meet at least two of the three criteria of pain at night, morning stiffness, pain lasting for at least 30 minutes following the initiation of movement. The participants consumed dry willow bark extract (393.24mg) tablets that could be taken up to two times daily with salicin content ranging from 120-240mg. The study lasted six weeks with a physician examination at week three

and six. To gauge effectiveness, the treating physician assessed tenderness of joints, restriction of movement, crepitation, swollen joints, and the severity of disease according to the Clinical Global Impression (CGI) five-point scale. In addition, participants rated their perceived effectiveness of treatment and the WOMAC questionnaire that assessed pain, stiffness, and physical function on week three and six. Lastly, tolerance was recorded after week three and six in the form of adverse effects reported by both participant and physician. Nine doctors and 139 patients participated in the study with 88 participants in the willow bark extract group, eight in the combination (willow bark extract + NSAIDs) group and 40 in the reference medication (NSAIDs only) group. The results showed that all groups saw improvements in symptoms after three weeks of treatment and greater improvements by the end of the study. On average, the reference group saw improvements in 8.49 days. while the willow bark extract group saw improvements in 13.52 days. After six weeks, there was a trend towards the willow bark extract bring more effective in decreasing pain depicted by the WOMAC score (willow bark extract -41.8%; reference medication: -32.4%) and stiffness (willow bark extract: -42.1; reference medication; -30.9%). In terms of effectiveness, treating physicians stated that the reference medication had a stronger and faster reaction after three weeks of treatment but after six weeks of treatment, the reference group was only slightly more effective in treating gonarthosis and coxarthrosis. Most of the patients (92.2%) in the willow bark extract group consumed the maximal dosage allowed (1.572g of extract with 240mg salicin) to combat pain and inflammation. The researchers concluded that willow bark extract, at the highest dose allowed, is comparable to NSAIDs in treating inflammation associated with nociceptor pain.

Uehleke and colleagues (2013) examined the effects of aqueous willow bark extract (STW 33-I) in the long term (>6 months) treatment of musculoskeletal disorders such as osteoarthritis or back pain. During this 24 week study there was no strict drug regimen. Participates could take STW 33-I (with 23-26% total salicin) alone or with other NSAIDs or

analgesic medication. Measurements were obtained at baseline and after 3,6,12,18, and 24 weeks. Primary measurements were a global pain assessed on a 0-100mm VAS, efficacy of treatment measured by the treating physician, safety, and tolerability of the willow bark extract. The patients were required to keep a daily diary where they self-rated their pain, documented any changes in pain or therapy and the dosage of STW 33-I and other medication consumed during the 24 weeks. In total, 436 participants with 58% having either osteoarthritis or back pain for at least five years participated in the study. At the beginning of the study all participants were taking the willow bark extract. By the end of the 24 weeks, 61.5% of the patients took no analgesic co-medication, 28.9% took NSAIDs, and 3.9% required a triple therapy of STW 33-I, NSAIDs and opioids. During the treatment period, patients experienced a significant ($p < 0.05$) and continuous pain relief. After three weeks of treatment, a clinically relevant pain reduction was observed with pain 45.6% lower than what it was at baseline. Remarkably, after 24 weeks of treatment, regarding symptoms, 60% of patients were completely or partly in remission. Based on the results, the authors concluded that willow bark extract had a mild effect as an analgesic and those suffering from mild or chronic pain could be treated with willow bark extract alone. They also suggested that physicians should consider starting a treatment regimen with willow bark extract alone and adding NSAIDs or opioids as needed.

2.3.3 Summary of "Effectiveness of Willow Bark in Decreasing Pain"

Willow bark may be a potential natural remedy for gonarthosis, coxarthrosis and other musculoskeletal disorders that result in pain. The consensus among researchers is that willow bark is either more effective (Beer & Wegener, 2008; Saller et al., 2008; Schmid et al., 2001) or just as effective (Chrubasik, Künzel, Model, et al., 2001; Uehleke et al., 2013) in decreasing pain compared to other NSAIDs or placebo. In contrast, (Biegert et al., 2004) concluded that the

standardized NSAID used to treat osteoarthritis, diclofenac, was more effective than willow bark in decreasing pain and increasing physical function. In addition, they found that willow bark was no more effective than a placebo pill in the treatment of pain. In the treatment of low back pain, rheumatoid pain, and other musculoskeletal disorders there is a trend of a dose dependent response (Beer & Wegener, 2008; Sigrun Chrubasik et al., 2000; Saller et al., 2008) in the alleviation of pain with 240mg of salicin being more effective than 120mg.

Due to the more observational nature most of these studies (Beer & Wegener, 2008; Chrubasik, Künzel, Black, et al., 2001; Saller et al., 2008; Uehleke et al., 2013) caution should be warranted with interpreting the results as most studies allowed the participants to continue taking NSAIDs with willow bark. Therefore, it is difficult to determine if the pain relief was due to willow bark alone or from the combination of willow bark with NSAIDs or opioids. More randomized, placebo-controlled studies should be done to confirm the effectiveness of willow bark on the alleviation of pain in those suffering from musculoskeletal disorders.

2.4 Adverse Events Associated with Willow Bark Compared to other NSAIDs

2.4.1 Willow Bark and Platelet Aggregation

Aspirin and other NSAIDS have a higher risk of adverse effects such as gastric ulcers, an increased risk of bleeding and gastrointestinal upset that is rarely observed with the consumption of standardized willow bark extract (Bonaterra et al, 2010). The long-term consumption of aspirin increases the risk of gastrointestinal bleeding and other bleeding disorders. Aspirin, when it blocks COX-1, inhibits the synthesis of platelet thromboxane A2 irreversibly impending the substrates access to its active site. (Catella-Lawson et al., 2001; Sostres & Lanas, 2011). Since

thromboxane A2 is required for the synthesis of new platelets, the consumption of aspirin inhibits platelet formation for the duration of the platelets 8-10 day lifespan (Cryer, 2010). The inhibition of platelet aggregation increases the chances of developing bleeding disorder. In addition, by preventing platelet aggregation, aspirin can enhance the bleeding potential in those who have asymptomatic gastrointestinal mucosal lesions (Vlachojannis et al., 2009). In comparison, naturally occurring salicylic acid does not function as an anticoagulant and does not inhibit platelet aggregation. Consuming willow bark instead of aspirin may decrease the risk of experiencing a bleeding disorder. In addition, willow bark may be able to be continued leading up to a surgical procedure unlike aspirin which is often stopped 7-14 days prior to the procedure. However, more research needs to be done to confirm this theory.

2.4.2 Reported Adverse Effects with Willow Bark

Compared to aspirin, willow bark is believed to have a lower toxicity due to its low level of salicylates (Vlachojannis et al., 2009). However, the data on willow back's toxicity is lacking in the literature (Catella-Lawson et al., 2001). According to the Food and Drug Administration (2003), willow bark is shown to be consumed for over three months without any adverse effects. In all the clinical trials published, only 5% of all participants had some sort of adverse effect from the consumption of willow bark and those reactions were mild (Anonymous, 2003). It appears that willow bark has a low incidence of adverse effects compared to aspirin due to the addition of other constitutes and the absences of acetylsalicylic acid. The co-active compounds (salicylates, flavonoids, catechol, and tannins) are not known to be harmful to the gastrointestinal mucosa compared to acetylsalicylic acid (Nikose et al., 2015). As of date, there is only one account of an individual experiencing anaphylaxis following the ingestion of a weight loss supplement containing willow bark. The female patient had a known allergy to acetylsalicylic acid and after

the administration of epinephrine, diphenhydramine, methylprednisolone, and volume resuscitation she recovered from the reaction (Boullata et al., 2003).

Many of the studies that examined the effectiveness of willow bark in treating conditions that resulted in pain and inflammation had a secondary analysis on the safety and tolerability of willow bark compared to a placebo or traditional NSAIDs. In the investigation done by Biegert and colleagues (2004) on efficacy and safety of willow bark in treating those with either osteoarthritis or rheumatoid arthritis, the authors reported 173 adverse effects in the osteoarthritis trial with most occurring in the Diclofenac group (n =84) compared to the placebo (n= 51) and willow bark (n = 38) groups. There were significantly ($p < 0.05$) 0more gastrointestinal adverse effects in the diclofenac group (n= 35) compared to the willow bark group (n= 7). After six weeks of consuming 100mg of diclofenac daily, the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT)had significantly increased. The increase in liver enzymes following Diclofenac consumption is a common occurrence due to the liver playing a role in the removal of this drug from the body (Nikose et al., 2015). In the rheumatoid trial both groups reported seven adverse events each with none of them being classified as serious.

Chrubasik et al (2000) examined the effects of a low dose (120mg salicin), a high dose (240mg salicin) or placebo on its ability to decrease low back pain. In this four-week investigation, participants could use tramadol up to 400mg per day as a rescue medication. Out of the 191 participants who completed this study, only nine participants reported an adverse event. In the high dose willow bark group two participants experienced dizziness or fatigue which were later linked back to the tramadol. In the low dose willow bark group, one participant experienced swollen eyes and pruritus that improved once willow bark was discontinued. In the placebo group, six participants experienced adverse events with three be contributed to the tramadol.

In a follow up study done by Chrubasik et al (2001a) on the economic effect of willow bark extract (Assalix) on the treatment of acute exacerbations of chronic non-specific back pain, the authors found that three causes of adverse skin reactions (exanthema and pruritus) were linked to the willow bark extract. In addition, 16 gastrointestinal complaints were documented with two complaints in participants receiving Assalix alone, four complaints in those receiving both Assalix and additional treatment and 10 in the group that received NSAIDs alone or cortisone treatment. A third study by Chrubasik and colleagues (2001b) compared the effects of willow bark extract (Assalix) and Rofecoxib (selective COX-2 inhibitor) on low back pain. After the four week treatment period, 23 adverse events occurred in the Assalix group and 27 in the Rofecoxib group. When the adverse events were broken down, 30 of those occurred within the gastrointestinal system (Assalix; n = 13; Rofecoxib: n = 17) with those in the Rofecoxib group being more severe in nature. In addition, there were five reports of a skin reactions in the Assalix group.

In an open observational study on the effectiveness of willow bark extract (Assalix) decreasing pain in participants with rheumatic pain, Saller, Melzer, and Felder (2008) found that 38 (4.3%) of the 204 participants reported 46 adverse events during the 6-8 week study. Predominantly of the adverse events occurred in the gastrointestinal system (3.1%), and the skin (1%). While none of the adverse events were severe, 30 participants discontinued with treatment. When the researchers cross examined the reported adverse events they found that 27 of the cases were likely caused by the treatment. In another open observational study conducted by Beer and Wegener (2008) on adults with coxarthrosis with hip pain or gonarthosis with knee pain, 14 of the 139 participants documented adverse events. When cross examined, only one adverse event was reported in the willow bark group, 11 were reported in the reference medication group (NSAID only) and two in the combination group (willow bark extract + NSAID). The type of adverse events experienced by the participants were not disclosed by the researchers. Both treating

physicians and participants considered willow bark to be superior in tolerability compared to the reference medication.

Uehleke et al (2013) examined the effectiveness of aqueous willow bark extract (STW 33-I) in the long term (>6 months) treatment of pain in those with osteoarthritis or back pain. This was one of the first studies to examine the tolerability of consuming willow bark on a long-term basis. The researchers evaluated the number of reported adverse events during the 24-week study. The researchers discovered that 176 adverse events were reported in 106 patients with 7 patients reporting a severe adverse effect. With further evaluation, the researchers concluded that none of the adverse events were related to the willow bark. When broken down into the treatment groups, 35.8% of the adverse events occurred in the willow bark monotherapy group, 54.5% occurred in the combination group (willow bark + NSAIDs) and 9.7% in the triple treatment group (willow bark + NSAIDs + opioids). The most reported adverse effects occurred in the gastrointestinal system such as upper abdominal pain or nausea. Overall, the researchers concluded that willow bark extract is safe for patients to take on a long term basis (> 6 months) as a monotherapy and combination with other NSAIDs or opioids in the treatment of musculoskeletal disorders.

Schmidt et al (2001) had participants with a confirmed diagnosis of knee or hip osteoarthritis consume a high dose of willow bark extract (240mg salicin per day) or placebo in a two-week double-blind randomized controlled study. During the investigation, participants were instructed to record any adverse events in their diary. At the end of the two-week treatment period, 16 participants (41%) in each group reported an adverse event. The most reported adverse effects were allergic skin reactions or gastrointestinal upset. Surprisingly, there were more reported adverse events in the placebo (n = 28) compared to that of the willow bark group (n = 17). Only one reaction was considered as clinical importance in the willow bark group in which the participant developed a skin rash near the end of the study and dropped out the of investigation. The participant had a medical history of reacting to various medications.

Akao and associates (2002) conducted an in vivo study in which they compared the effects of salicin, saligenin, sodium alicylate, and pure water on gastrointestinal lesions in rats. The compounds were orally administered at a dose of 1, 2.5 and 5m/mol/kg body weight. When examining lesions, the authors found the oral administration of up to 5mmol/kg of sodium salicylate and saligenin promoted the development of injuries to the mucosa of the stomach such as bleeding, serious wounds, and gastric lesions. A higher dose of sodium salicylate consumed resulted in greater gastric injury. In comparison, salicin, regardless of dosage, did not produce any indications of a gastric injury. In the rats that consumed salicin, the degree of injury was comparable to that of rats who received just water. It was concluded that salicin from willow bark could be an alternative medication used to treat musculoskeletal conditions in individuals with a history of developing gastric lesions from consuming aspirin or other NSAIDs.

2.4.3 Conclusion of Willow Barks Adverse Effects

Based on the review of literature, it can be concluded that willow bark extract may be tolerated better with less gastrointestinal effect than NSAIDs or aspirin due to the low levels of salicin and abundance of polyphenols and flavonoids which target inflammatory mediators in a different manner. Compared to NSAIDs, the adverse effects appear to be mild with the most common reported being minor gastrointestinal upset. Due to apparent low toxicity, many physicians in Europe often recommend the use of willow bark in conjunction with aspirin to enhance the treatment effects in hopes of decreasing the risk of adverse reactions (Altinterim, 2013). It is important to note that most of the investigations allowed the participants to continue with their normal use of NSAIDs or allowed the use of opioids as a recue medication while taking willow bark extract. Therefore, the exact number and degree of adverse effects due to willow bark extract is unknown.

CHAPTER III

METHODOLOGY

3.1 Introduction

A double-blind randomized placebo-controlled study design was utilized to determine the effects of white willow bark (WWB) on parameters of delayed onset muscle soreness (DOMS) and if WWB could maintain athletic performance following an exhaustive lower body resistance training session. To investigate the effects of WWB on DOMS and athletic performance, participants completed an exhaustive lower body resistance training session to induce DOMS followed by a five day supplementation period in which the participants ingested either WWB or a placebo. Prior to inducing DOMS, baseline data for parameters of DOMS and athletic performance was collected and tracked the changes of these variables over the course of DOMS development and recovery. Statistical analysis was completed to compare the means between the WWB and placebo group to determine the effect of WWB on parameters of DOMS and its ability to maintain athletic performance. This investigation was approved by the Oklahoma State University Institutional Review Board for human participant research.

3.2 Participants

Twenty-five participants volunteered for this investigation. All participants were required to be healthy and free from any signs or symptoms of disease, without any musculoskeletal injury, previous surgery within the last six months involving the hip, low back, knee, or ankle. In addition, had to be free from any type of arthritis (i.e., osteoarthritis, gout, rheumatoid arthritis) or have chronic back pain. The participants could not be participating in a lower body resistance training program on a regular basis (at least 3 days a week for the last 3 months). During this investigation, participants were required to refrain from participating in any exercise or physical activity program involving the lower body. Furthermore, participants were asked to refrain from taking any NSAIDs, analgesics, corticosteroids, or any type of nutritional aid that could interfere with the potential therapeutic actions of WWB. Those who were taking medication known to interfere with WWB (i.e., anticoagulants, beta blockers, diuretic, methotrexate, or phenytoin) and those with a known allergy or sensitivity to salicylates such as aspirin were excluded from this investigation. Following enlisting the participants, their first visit to the Applied Neuromuscular Lab was scheduled. During the first visit, participants completed a health history questionnaire (Appendix A) to verify they met the inclusion criteria for this investigation. Then the researcher and participant discussed the IRB informed consent form and the requirements of the study and the participant expectations. Afterwards, the participants completed a familiarization four repeated counter-movement jump session and became familiar with the visual analog scale (VAS) (Appendix B). Following the completion of session one, each participant was randomly place in either the WWB group (n= 11) or placebo group (n = 14).

3.3 Study Design

The current investigation included four visits to the Neuromuscular Physiology Lab and five days of supplementation as outlined in Figure 3. Session one consisted of equipment

familiarization, height, weight, and the competition of pre-participation paperwork. After session one, participants were randomly assigned one of the treatment groups. During session two, baseline measurements parameters of DOMS (muscle soreness, mid-thigh circumference, and pressure pain threshold) were measured. In addition, baseline athletic performance was measured with a four repeated counter-movement jump test in which jump height, ground-contact time and peak power and peak velocity was recorded. After the collection of baseline data, participants took part in a lower body resistance training session to induce DOMS. After the completion of the training session and resting for 10 minutes, the parameters of DOMS were measured again followed by the four repeated counter-movement jump test to measure the immediate response to muscle fatigue. Participants were provided with a brown container that held their first dose and additional five day supply of WWB supplement or placebo and given instructions for ingesting their randomly assigned treatment. Participants ingested their first dose (two capsules) of either WWB or placebo with water and were instructed to not take another dosage until the next morning. Beginning the morning after session two, participants began the five day supplementation period. Participants were asked to take two capsules of their assigned treatment morning, noon, and night with food. Each morning during the supplementation period participants rated their muscle soreness within 30 minutes of waking. Participants were required to report back to the Neuromuscular Physiology lab on day three (72 hrs.) and day 6 (post) a repeated measurement of parameters of DOMS and athletic performance. All testing procedures were performed at a consistent time each session.

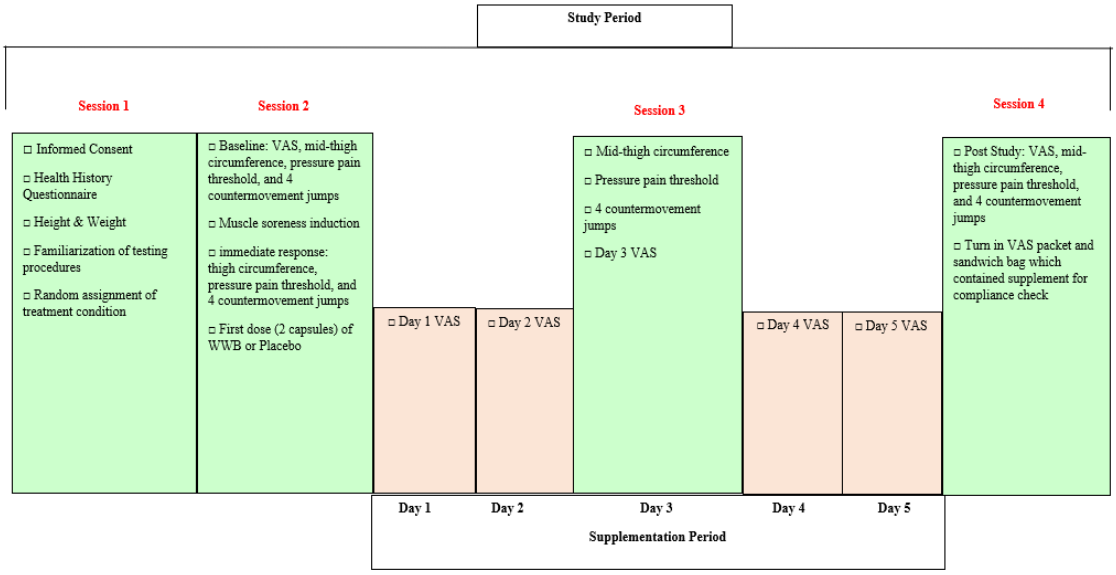

Figure 3. Experimental Design. VAS: visual analog scale for assessment of DOMS; WWB; white willow bark.

3.4 Instruments and Procedures

3.4.1 Height and Weight

During the first visit to the Neuromuscular Physiology Lab, weight, and height were measured. Weight was measured on a floor scale (CPW Plus 150; Adam Equipment™, Oxford, CT, USA) and height was measured with a height beam on a physician scale (Weight-Beam Eye-Level physician Scale; Detecto, Webb City, MO, USA). For this investigation, the participant's weight was used to calculate the percentage of body weighted the used during the exhaustive lower body resistance training session to induce DOMS.

3.4.2 Visual Analog Scale

A visual analog scale (VAS) consists of a 100mm line with polar extremes (none and extreme) to assess pain. This subjective scale has been used in many various studies and is considered a valid and reliable way to assess pain and soreness (Hoseinzadeh et al., 2015; Pumpa et al., 2013; Wheeler & Jacobson, 2013). The baseline VAS was measured during session two before participants completed the lower body resistance training session to induce DOMS. Participants were asked to rate their level of pain or discomfort for their quadriceps, hamstrings, gastrocnemius, and gluteal muscles. Each participant was sent home with a five day VAS packet with instructions. Each day during the supplementation period, participants rated their level of pain or discomfort for the quadriceps, hamstrings, gastrocnemius, and gluteal muscles each morning within 30 minutes of waking. On day six (session four), participants brought their VAS packet to their last session to turn in to their primary investigator for analysis and they completed their final (post supplementation) VAS.

3.4.3 Mid-Thigh Circumference

Participants were asked to place one foot on a chair, so both the knee and hip were at 90° measured by a goniometer. Using a Gulick tape measure, the midpoint between the inguinal crease and the proximal border of the patella was measured. Using a semi-permanent marker, a small dot was placed at the midpoint where mid-thigh circumference was to be measured. With the zero of the Gulick tape measure placed on the small dot, thigh circumference was measured to the nearest 0.1cm and recorded. Three measurements were obtained, and the average was recorded. This was completed for both right and left mid-thigh. Mid-thigh circumference was measured at baseline, immediately following exercise, day three (72hrs.) and day six (post).

3.4.4 Pressure Pain Threshold

A handheld algometer (Wagner Force Ten ™ Digital Force Gage; Wagner Instruments, Greenwich, CT, USA) was used to measure pressure pain threshold. A handheld algometer has been shown to be a valid and reliable tool in evaluating pressure pain threshold (Kinser et al., 2009; Waller et al., 2015). Participants were asked to sit in a chair with feet flat on the ground and knees at 90° measured with a goniometer. Using the same spot where mid-thigh circumference was measured (the midpoint between the inguinal crease and the proximal border of the patella) the handheld algometer was placed on the dot. Participants were asked to report when "pressure started to feel uncomfortable." Pressure was applied in a slow downward manner and at the participants response of "stop" the measurement was recorded to the nearest 0.01oz. The average of three measurements were obtained for both right and left mid-thighs while alternating thighs after each measurement. Pressure pain threshold was measured at baseline, immediate response, day three (72 hrs.) and day six (post).

3.4.5 Four Repeated Countermovement Jumps

A four repeated countermovement jump test was used to determine the detrimental effects of DOMS on performance and if WWB could maintain athletic performance. Participants wrapped the Tendo Unit (Tendo Sports, Trencin, Slovak Republic) strap around their waist. The Tendo Unit measured both peak power and peak velocity during the four repeated countermovement jumps. When instructed, participants stepped on the switch mat (Just Jump; Pro Biotics Inc, Huntsville, AL, USA). The participants were asked to stand upright on the mat with the weight distributed on both feet with their hands on their hips. When ready, participants squatted to approximately 90° and immediately jumped vertically as high as possible landing back on the mat with both feet at the same time. Immediately after their feet landed on the mat they jumped vertically as high as possible once again. The participants completed four

countermovement jumps in a row with their hands always remaining on their hips. The average ground contact time and the average vertical jump height were recorded. The average vertical jump height was converted to metric units (centimeters) before data analysis. The participants completed this test at baseline, immediate response, day three (72hrs.) and day six (post).

3.4.6 Fatiguing Protocol

Following the collection of baseline data, participants took part in a lower body resistance training session to induce DOMS. After a five minute warm up on a cycle ergometer, participants first performed five sets of 10 lunges at 40% of their body weight (BW) with a one minute rest between sets. Participants performed lunges with alternating legs. Participants stood straight with a dumbbell in each hand (20% BW right and 20% BW left) with their feet shoulder width apart. When ready, the participant took a large step forward so the thigh of the lead foot was located directly above or slightly in from the toes with the opposite knee slightly behind the hips and slightly bent (about one inch above the level the floor). Using the power of the lead leg, the participant pushed backwards so that both feet were together again. These steps were repeated with the opposite leg until all sets and repetitions were completed. Following the completion of lunges, the participant completed three sets to fatigue on the seated leg press (Hammer Strength Select Seated Leg Press; Life Fitness Inc, Park, IL, USA) at 75% of their body weight with a one minute rest between each set. To standardize the protocol during the leg press, a metronome (Metronome app by ONYX Apps; Apple Inc, Cupertino, CA) was set at 60 beats per minute (Selkow et al., 2015). Fatigue was determined when participants could no longer lift the weight or could no longer keep up with the metronome on three consecutive counts.

3.4.7 Treatment Conditions

Participants were randomly assigned to either the WWB or placebo group using a computerized randomized scheme. WWB was purchased from the company Puritan's Pride. Immediately following the collection of the immediate response data, participants were handed a brown container that held a sandwich bag with their supplements and instructions on how to take their supplement. Giving participants a brown container kept the researcher from knowing which group the participant was placed in. Once the participants received their container, they ingested their first dose (two capsules) of WWB or placebo with water. Beginning the morning after session two, participants began the five day supplementation period. During the supplementation period, participants in the WWB group took two capsules containing 133mg of willow bark extract three times daily for a total of 798mg per day. The placebo group took two capsules containing powder sugar three times daily. Participants in both treatment conditions were instructed to ingest two capsules in the morning, noon, and evening with food to decrease the risk of adverse effects. Each morning during the supplementation period, participants received a text message reminding them to take their supplement and to fill out their VAS. On the last session (day six), participants were required to bring back container that contained the supplement for a compliance check. A compliance of 80% was set for data to be included in the statistical analysis. This percentage was used in a previous that examined the effects of a natural supplement on DOMS (Jäger et al., 2019).

3.4.8 Statistical Analysis

Prior to analysis, box and whisker plots were used to determine and eliminate any outliers and the data was checked for normality with the Shapiro-Wilks test. Levene's test was performed to evaluate the homogeneity of variances. Furthermore, Mauchley's test was applied to evaluate the assumption of sphericity for repeated measures ANOVA. If the assumption was sphericity

was violated, the Greenhouse-Geisser was used. Statistical analysis was performed using SPSS statistical software (Version 27.0, IBM Corp, Chicago, IL, USA). Twelve two-way repeated measure ANOVAs were utilized in this investigation and included the following:

1. Vertical Jump Height: Time [Baseline, Immediate, Day 3, Post] X Treatment (Placebo vs. WWB)
2. Ground Contact: Time [Baseline, Immediate, Day 3, Post] X Treatment (Placebo vs. WWB)
3. Peak Power: Time [Baseline, Immediate, Day 3, Post] X Treatment (Placebo vs. WWB)
4. Peak Velocity: Time [Baseline, Immediate, Day 3, Post) X Treatment (Placebo vs. WWB)
5. Right Thigh Circumference: Time [Baseline, Immediate, Day 3, Post) X Treatment (Placebo vs. WWB)
6. Left Thigh Circumference: Time [Baseline, Immediate Day 3, Post) X Treatment (Placebo vs. WWB)
7. Right Pressure Pain Threshold: Time [Baseline, Immediate, Day 3, Post) X Treatment (Placebo vs. WWB)
8. Left Pressure Pain Threshold: Time [Baseline, Immediate, Day 3, Post) X Treatment (Placebo vs. WWB)
9. VAS Calf: Time [Baseline, Day 1, Day 2, Day 3, Day 4, Day 5, Post) X Treatment (Placebo vs. WWB)
10. VAS Quadriceps: Time [Baseline, Day 1, Day 2, Day 3, Day 4, Day 5, Post) X Treatment (Placebo vs. WWB)
11. VAS Hamstrings: Time [Baseline, Day 1, Day 2, Day 3, Day 4, Day 5, Post) X Treatment (Placebo vs. WWB)

12. VAS Gluteal Muscles: Time [Baseline, Day 1, Day 2, Day 3, Day 4, Day 5, Post) X Treatment (Placebo vs. WWB)

The main effects were analyzed for all variables that showed no significant interaction effects. For a significant main effect, all pairwise comparisons were examined with a Bonferroni correction. Cohen's d was calculated to determine effect size (d) between days and interpreted as 0.2, 0.5 and 0.8 for small, medium, and large effects. Participant demographics were compared using an independent-t test. The alpha (α) level was set at 0.05. All results are expressed as mean ± standard deviation (SD).

CHAPTER IV

RESULTS

4.1 Descriptive Statistics

Twenty-five healthy males (n = 10) and females (n =15) took part in this investigation. Fourteen were randomly placed in the placebo group (male: 6; female: 8) and 11 in the WWB (male: 4; female: 7) group. The results of the independent t-test revealed no significant differences ($p > 0.05$) between the groups in age, height, weight, and body mass index (BMI) (Table 1). All 25 participants reported no adverse effects during the investigation. The compliance rate at the end of the study was comparable between groups. The placebo group had a compliance of 98.71% and the WWB group had a compliance of 98.18%.

Table 1. Demographic Data

	Placebo	**WWB**	***p* - value**
Age (yrs.)	19.93 ± 10.29	20.37 ± 1.29	0.316
Height (cm)	170.91 ± 10.29	168.97 ± 10.22	0.643
Weight (kg)	74.54 ± 17.51	72.86 ± 12.30	0.787
BMI (kg/m^2)	25.35 ± 5.37	25.57 ± 4.75	0.918

Mean ± SD; yrs.: years; cm: centimeters; kg: kilograms; kg/m^2 kilogram per meter squared; WWB: white willow bark; BMI: body mass index.

4.2. Muscle Soreness and Discomfort

4.2.1. Hamstring Muscle Soreness

The results revealed no significant hamstring muscle soreness and condition interaction (p > 0.05). However, there was a significant main effect of time on hamstring muscle soreness F (1.82, 32.82) = 24.250, p < 0.001 (Tables 2-3, Figure 4)

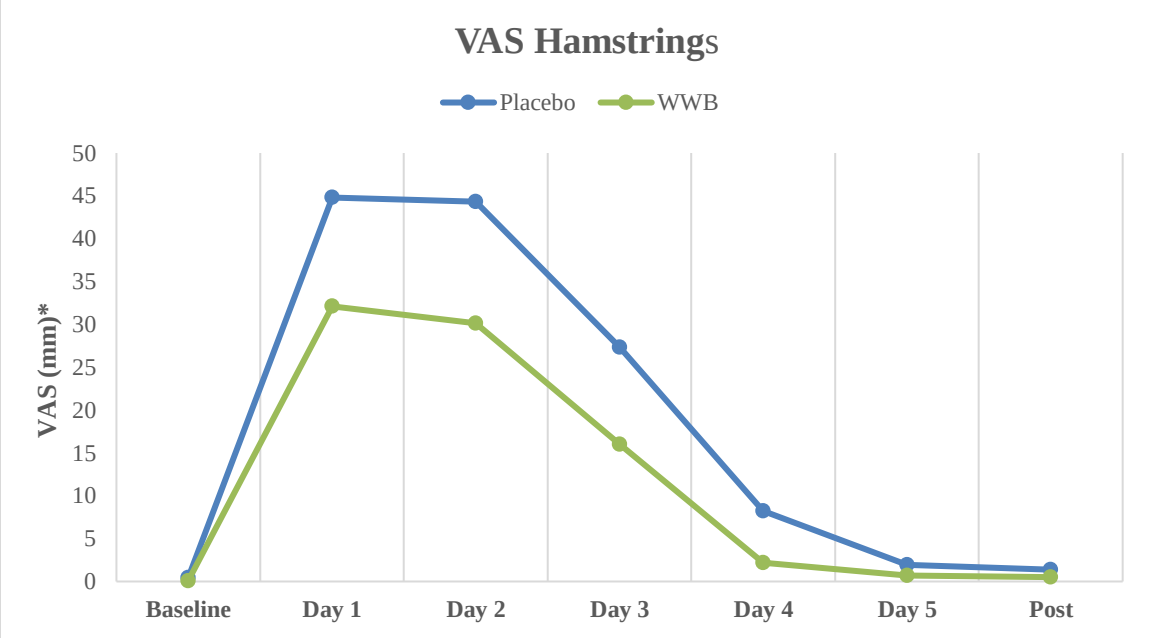

Figure 4. *Comparison of hamstring muscle soreness for participants in both the WWB and placebo groups over time.*Significant main effects of Time (collapsed across groups), VAS: visual analog scale; mm: millimeters; WWB: white willow bark.*

4.2.2. Gluteal Muscle Soreness

The results revealed no significant gluteal muscle soreness and condition interaction (p > 0.05). However, there was a significant main effect of time on gluteal muscle soreness F (2.82, 50.82) = 102.08, p < 0.001. (Tables 2-3, Figure 5).

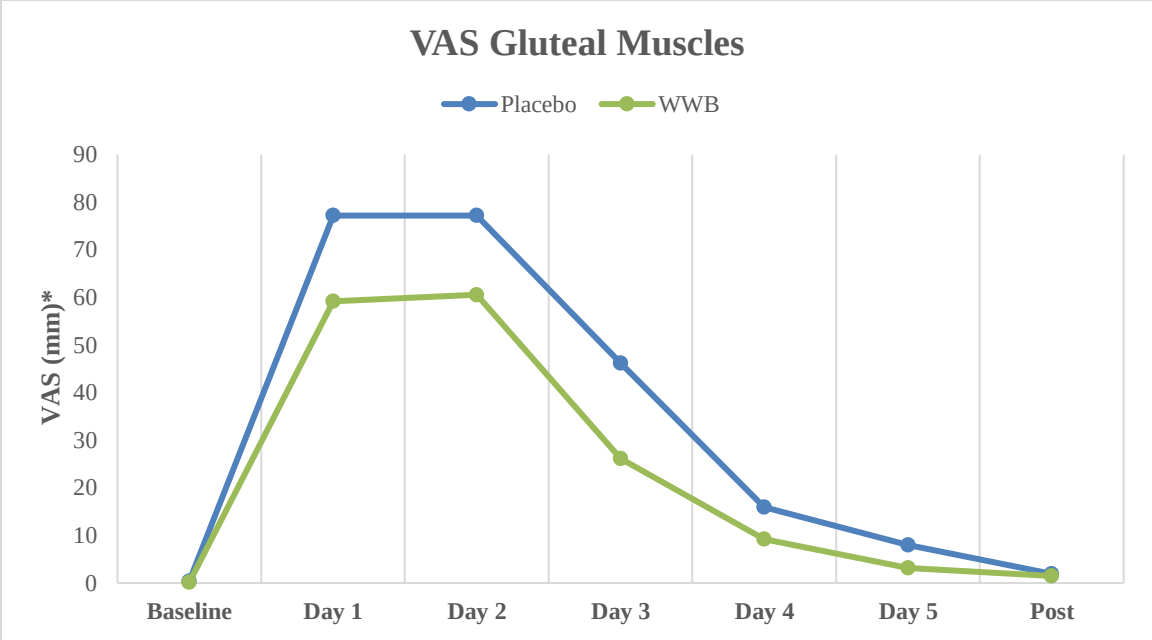

Figure 5. *Comparison of gluteal muscle soreness for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups), VAS: visual analog scale; mm: millimeters; WWB: white willow bark.*

4.2.3. Gastrocnemius Muscle Soreness

The results revealed no significant gastrocnemius muscle soreness and condition interaction ($p > 0.05$). However, there was a significant main effect of time on gastrocnemius muscle soreness $F(1.797, 34.142) = 11.515$, $p < 0.001$ (Tables 2-3; Figure 6).

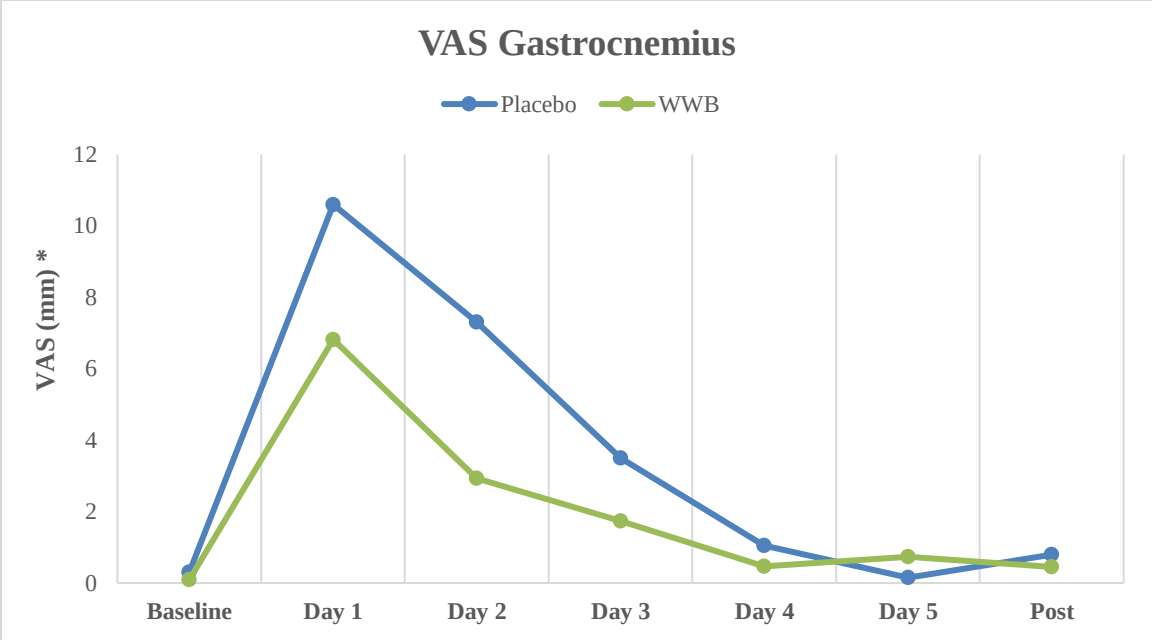

Figure 6 *Comparison of gastrocnemius muscle soreness for participants in both the WWB and placebo groups over time. *Significant main effects of time (collapsed across groups), VAS: visual analog scale; mm: millimeters; WWB: white willow bark.*

4.2.4. Quadriceps Muscle Soreness

The results revealed no significant quadriceps muscle soreness and condition interaction ($p >$ 0.05). However, there was a significant main effect of time on quadriceps muscle soreness F (2.654, 55.541) = 65.422, $p < 0.001$ (Tables 2-3; Figure 7).

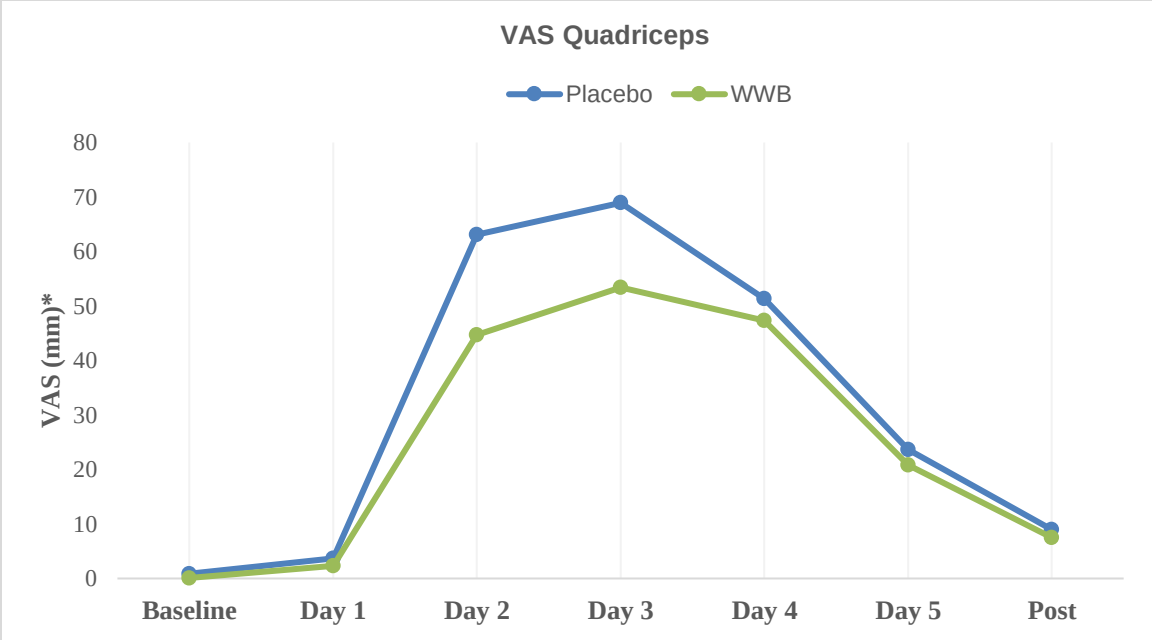

Figure 7. *Comparison of quadriceps muscle soreness for participants in both the WWB and placebo groups over time.*Significant main effects of time (collapsed across groups), VAS: visual analog scale; mm: millimeters; WWB: white willow bark.*

Table 2. VAS for Hamstring, Gluteal, Gastrocnemius, Quadriceps Muscles*

Hamstrings							
	Baseline[bcd]	**Day 1[aefg]**	**Day 2[aefg]**	**Day 3[aefg]**	**Day 4[abfg]**	**Day 5[bcd]**	**Post[bcd]**
Placebo	0.45 ± 0.50	44.80 ± 26.96	44.30 ± 29.68	27.30 ± 24.40	8.20 ± 9.14	1.95± 3.07	1.35 ± 1.23
% Diff Prev. Day		9855.56%	-1.12%	-38.37%	-69.96	-76.22%	-30.77
WWB	0.10 ± .32	32.10 ± 28.61	30.11± 35.04	16.02± 20.24	3.20 ± 9.14	0.70 ± 1.16	0.50 ± 1.27
% Diff Prev. Day		3200.00%	-6.20%	-46.80%	-80.02%	-78.13%	-28.57%
Difference (mm)	0.35	12.70	14.19	11.28	5.0	1.25	0.85
Gluteal							
	Baseline[bcde]	**Day 1[adefg]**	**Day 2[adefg]**	**Day 3[abcefg]**	**Day 4[abcdfg]**	**Day 5[bcde]**	**Post[bcde]**
Placebo	0.41 ± 0.49	77.18 ± 13.66	77.18 ±17.82	46.18 ± 26.47	15.91 ± 16.90	7.95 ± 11.77	1.91 ± 4.75
% Diff Prev. Day		18724.39%	0.00%	-40.17%	-65.55%	-50.03%	-75.97%
WWB	0.11± .33	59.22 ± 28.27	60.56± 26.88	26.11 ± 21.50	9.17 ± 13.70	3.11 ± 5.4	1.50 ± 2.47
% Diff Prev. Day		53736.36%	2.26%	-56.89	-64.88%	-66.09%	-51.77%
Difference (mm)	0.30	17.96	16.62	20.07	6.74	4.84	0.41
Gastrocnemius							
	Baseline[b]	**Day 1[aefg]**	**Day 2**	**Day 3**	**Day 4[b]**	**Day 5[b]**	**Post[b]**
Placebo	0.30 ± .35	10.60 ± 10.00	7.30 ± 9.34	3.50± 5.25	1.05 ± 2.48	0.15 ± 0.34	0.80 ± 1.11
% Diff Prev. Day		3433.33%	-31.13%	-52.05%	-70.00%	-85.71%	81.25%
WWB	0.09 ± .30	6.82 ± 9.18	2.93 ± 4.02	1.74 ± 3.43	.46 ± 1.21	0.73 ± 1.10	0.45 ± 1.11
% Diff Prev. Day		7477.78%	-57.04%	-40.61%	-73.56%	58.70%	-38.36%
Difference (mm)	.21	3.78	10.04	4.37	.59	.58	.35
Quadriceps							
	Baseline[bcedf]	**Day 1[cdef]**	**Day 2[abfg]**	**Day 3[abefg]**	**Day 4[abfg]**	**Day 5[abcdeg]**	**Post[acdef]**
Placebo	0.88 ± 1.17	3.73 ± 5.54	63.08 ± 24.79	68.93 ± 27.51	51.38 ± 25.01	23.69±21.41	9.02 ± 10.84
% Diff Prev. Day		323.86%	1591.15%	9.27%	-25.46%	-53.89	-61.92%
WWB	0.10 ± .54	2.31 ± 3.58	44.70± 33.60	53.40 ± 31.43	47.30 ± 24.73	20.80 ±21.41	7.50 ± 8.41
% Diff Prev. Day		221.00%	1835.06%	19.46%	-11.42%	-56.03%	-63.94%
Difference (mm)	0.78	2.31	18.38	15.53	4.08	2.89	1.52

*Mean ± SD; * significant main effect of time (collapsed across groups) ($p < 0.05$); WWB: white willow bark; mm: millimeters.*

a: a significant time difference from baseline
b: a significant time difference from day 1
c: a significant time difference from day 2
d: a significant time difference from day 3
e: a significant time difference from day 4
f: a significant time difference from day 5
g: a significant time difference from post

Table 3. Effect Size (*d*) Between Days for Subjective Muscle Soreness

	BL & D1	BL & D2	BL & D3	BL & D4	DL & D5	BL & D6	D1 & D2	D1 & D3	D1 & D4	D1 & D5	D1 & Post	D2 & D3	D2 & D4	D2 & D5	D2 & Post	D3 & D4	D3 & D5	D3 & Post	D4 & D5	D4 & Post	D5 & Post
Hamstrings	1.98	1.77	1.36	.97	0.67	0.58	.03	.45	1.55	1.88	1.94	0.45	1.43	1.71	1.76	.96	1.27	1.32	0.70	0.85	0.34
Gluteal	4.30	3.81	2.03	1.15	0.91	0.32	.001	1.01	2.54	3.54	4.12	1.05	2.36	3.20	3.66	1.03	1.60	1.92	0.58	0.98	0.61
Gastrocnemius	1.36	0.68	0.47	0.53	0.52	0.65	0.08	0.45	1.24	1.30	1.87	0.27	0.62	0.65	0.64	0.40	0.44	0.42	0.22	0.12	0.14
Quadriceps	2.78	3.10	2.80	1.42	1.08	0.82	0.30	0.40	1.37	2.28	2.68	0.71	1.67	2.60	2.99	0.99	1.92	2.35	0.84	1.28	0.78

BL: baseline; D1: day 1; D2; Day 2; D3; day 3; D4: day 4; D5;

4.3 Pressure Pain Threshold

The results revealed no significant pressure pain threshold and condition interaction for both the left and right mid-thighs ($p > 0.05$). However, there was a significant main effect of time for the right mid-thigh, $F(3, 60) = 3.399$, $p = 0.02$ (Table 2, Figure 8). In comparison, there was no significant main effect of time for the pressure pain threshold for the left mid-thigh ($p = 0.207$) (Tables 4-5; Figure 9).

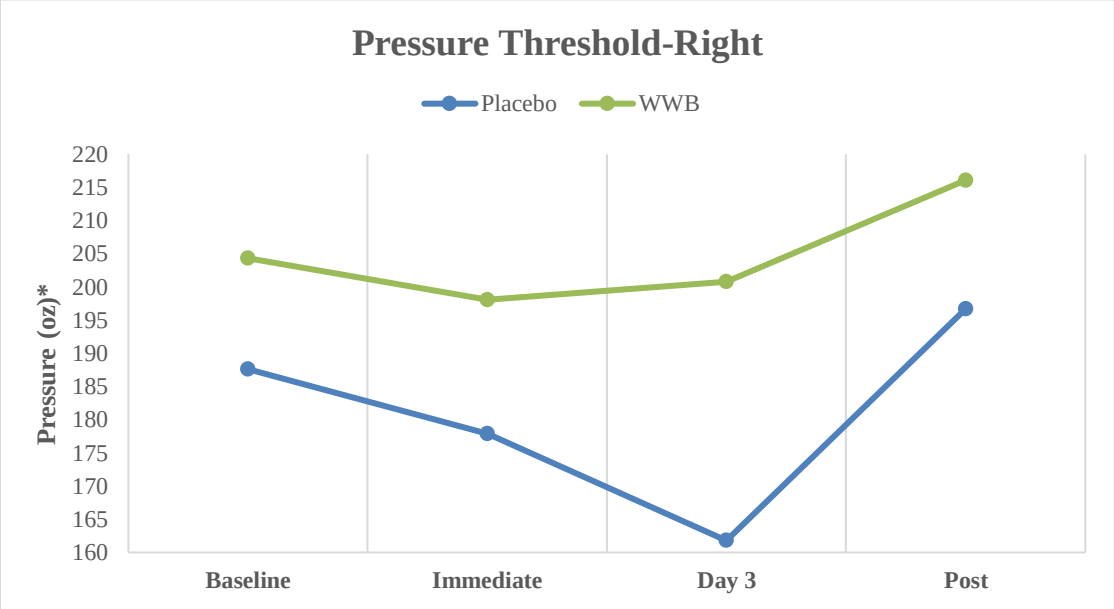

Figure 8. *Comparison of right thigh pressure threshold for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups); oz.: ounces.*

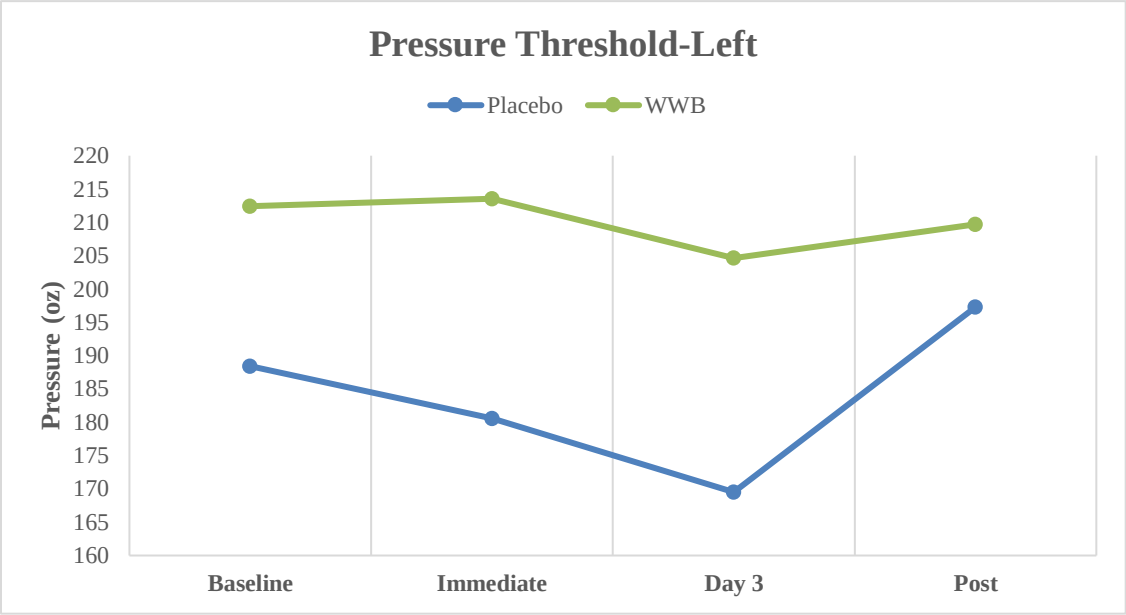

Figure 9: *Comparison of left thigh pressure threshold for participants in both the WWB and placebo groups over time. oz.: ounces*

4.4 Mid-Thigh Circumference

The results revealed no significant mid-thigh circumference and condition interaction for both the left and right mid-thighs ($p > 0.05$). However, there was a significant main effect of time for the right mid-thigh circumference, $F(3, 66) = 7.135$, $p < 0.001$ (Table 2, Figurer 10). Furthermore, there was a significant main effect for the left mid-thigh circumference, $F(3, 69) = 15.784$, $p < 0.001$ (Tables 4-5; Figure 11).

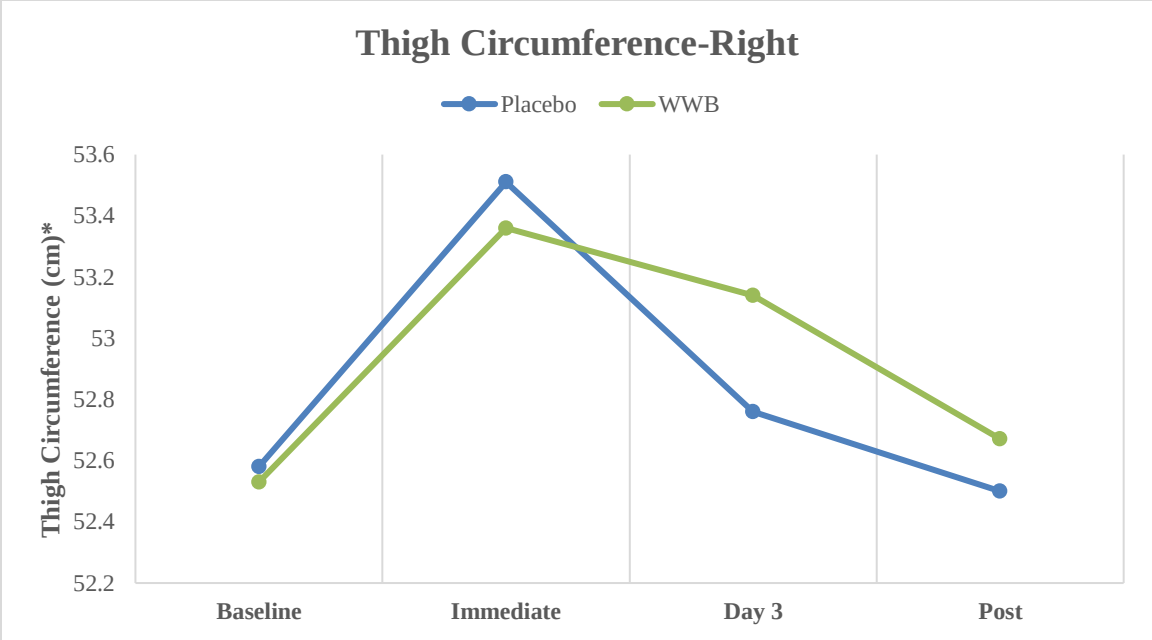

Figure 10. *Comparison of right thigh circumference for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups), VAS: visual analog scale; cm: centimeters.*

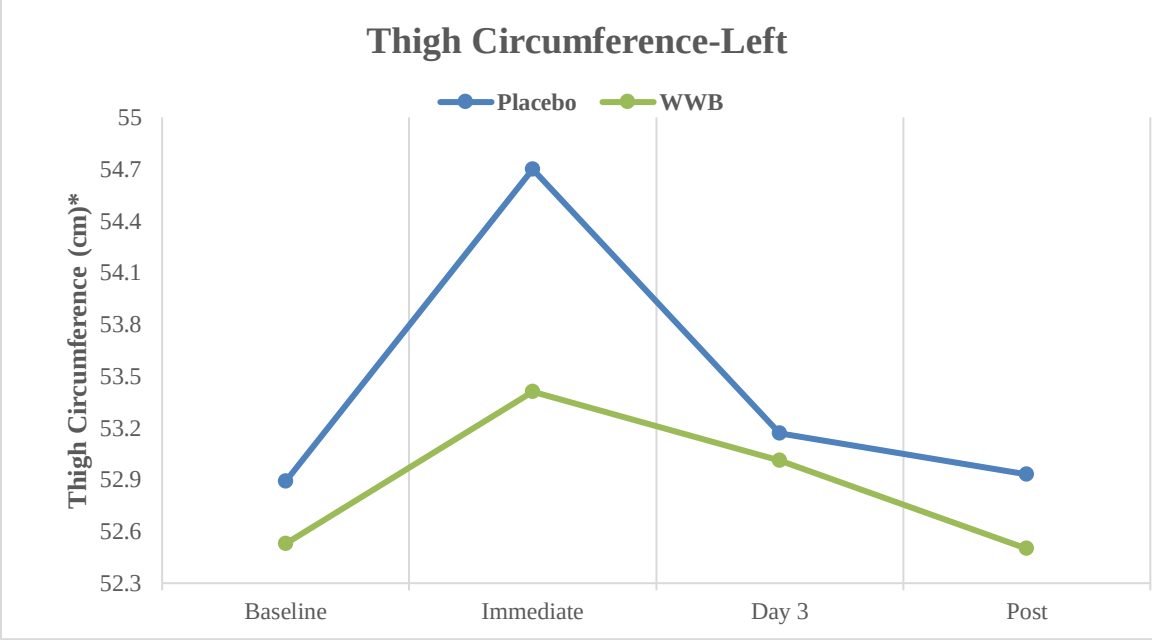

Figure 11. *Comparison of left thigh circumference for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups); cm: centimeter*

Table 4. Parameters of Muscle Damage Measured Prior and Following DOMS

Right Thigh Circumference (cm)*		**Placebo**	**WWB**
Baseline[b]	Mean	52.58 ± 5.25	52.53 ± 4.26
Immediate[ad]	Mean % diff pre	53.51 ± 5.40 1.77%	53.36 ± 3.99 1.58%
Day 3	Mean % diff pre	52.76 ± 5.26 0.34%	53.14 ± 4.55 1.16%
Post[b]	Mean % diff pre	52.50 ± 5.30 0.15%	52.67 ± 4.43 0.27%
Left Thigh Circumference (cm)*			
Baseline[b]	Mean	52.89 ± 5.42	52.53 ± 4.43
Immediate[acd]	Mean % diff pre	54.07 ± 5.78 2.23%	53.41 ± 3.89 1.68%
Day 3[b]	Mean % diff pre	53.17 ± 5.30 1.89%	53.01 ± 4.18 0.91%
Post[b]	Mean % diff pre	52.93 ± 5.97 0.08%	52.50 ± 4.32 -0.06%
Right Pressure Threshold(oz)*			
Baseline	Mean	187.61 ± 35.68	204.30 ± 46.94
Immediate	Mean % diff pre	177.86 ± 51.28 -5.20%	198.07 ± 50.96 -3.05%
Day 3[d]	Mean % diff pre	161.79 ± 44.50 -13.76%	200.81 ± 44.59 -1.71%
Post[c]	Mean % diff pre	196.69 ± 45.89 4.84%	216.07 ± 60.31 5.76%
Left Pressure Threshold (oz)			
Baseline	Mean	188.40 ± 37.41	212.46 ± 27.08
Immediate	Mean % diff pre	180.56 ± 30.09 -4.16%	213.54 ± 42.15 0.51%
Day 3	Mean % diff pre	169.51 ± 53.38 -10.03%	204.63 ± 35.16 -3.69%
Post	Mean % diff pre	197.27 ± 45.03 4.71%	209.67 ± 27.71 -1.31%

*Mean ± SD; * significant main effect of time (collapsed across groups) ($p < 0.05$); WWB: white willow bark; sec: seconds; oz.: ounces.*

a: a significant time difference from baseline
b: a significant time difference from immediate
c: a significant time difference from day 3
d: a significant time difference from post

Table 5. Effect Size (*d*) Between Days for Parameters of DOMS

	BL & IR	BL & D3	BL & Post	IR & D3	IR & Post	D3 & Post
PPT-R	0.12	0.10	0.32	0.01	.40	0.37
PPT-L	0.01	0.24	0.16	0.21	0.11	0.36
TC-R	0.19	0.17	0.01	0.008	0.18	0.16
TC-L	0.21	0.06	0.001	0.15	0.20	.05

PPT-R: pressure pain threshold for right mid-thigh; PPT-L: pressure pain threshold for left mid-thigh; TC-R: right mid-thigh circumference; TC-L left mid-thigh circumference; BL: baseline; IR: immediate response; D3: day

7.5 Athletic Performance

4.5.1 Jump Height

The results revealed no significant jump height and condition interaction ($p > 0.05$). However, there was a significant main effect for time F (1.916, 42.142) = 26.479, $p < 0.001$ (Tables 6-7; Figure 12)

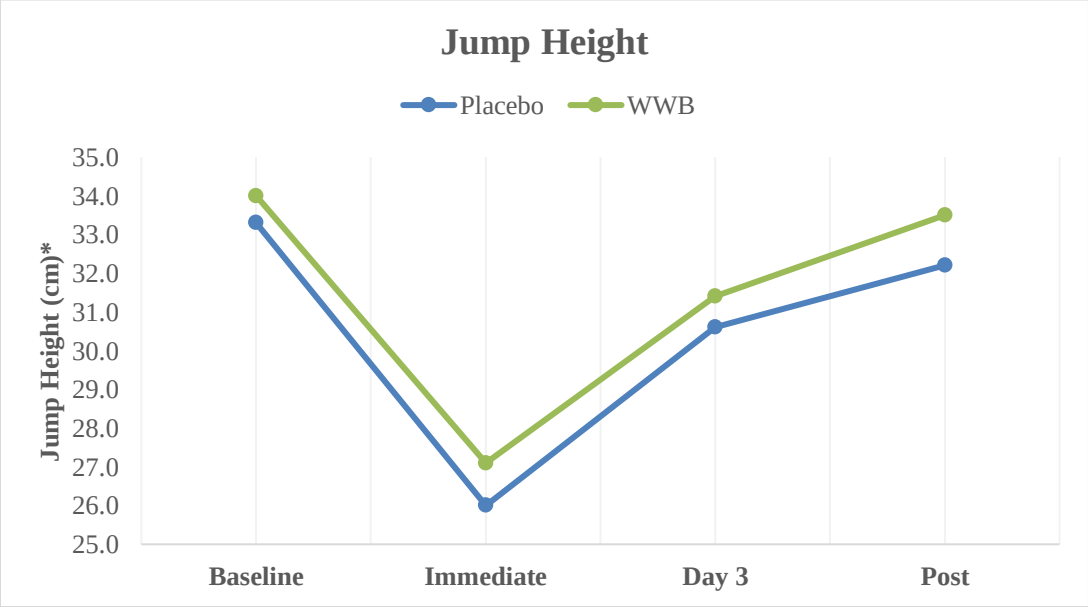

Figure 12. *Comparison of jump height for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups); cm: centimeters.*

4.5.2 Ground Contact Time

The results revealed no significant ground contact time and condition interaction ($p > 0.05$). However, there was a significant main effect of time F (1.823, 40.115) = 7.743, $p = 0.002$ (Table 6-7, Figure 13).

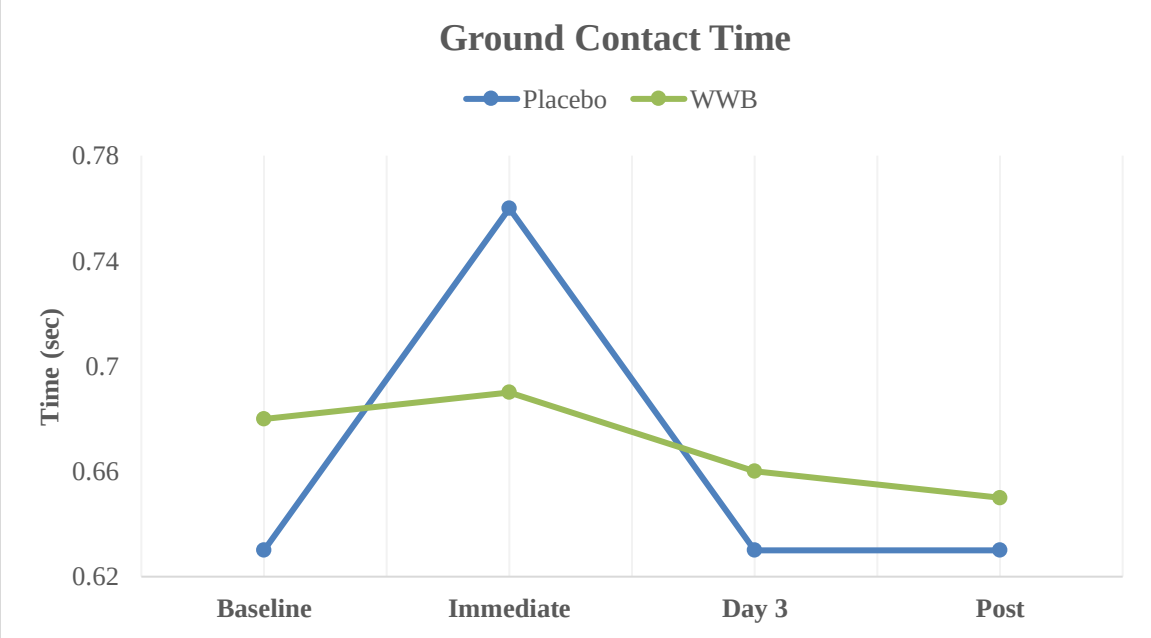

Figure 13. *Comparison of ground contact time for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups); sec: seconds*

4.5.3 Peak Power

The results revealed no significant peak power and condition interaction ($p > 0.05$). However, there was a significant main effect of time F (3, 66) = 22.947, $p < 0.001$ (Tables 6-7, Figure 14).

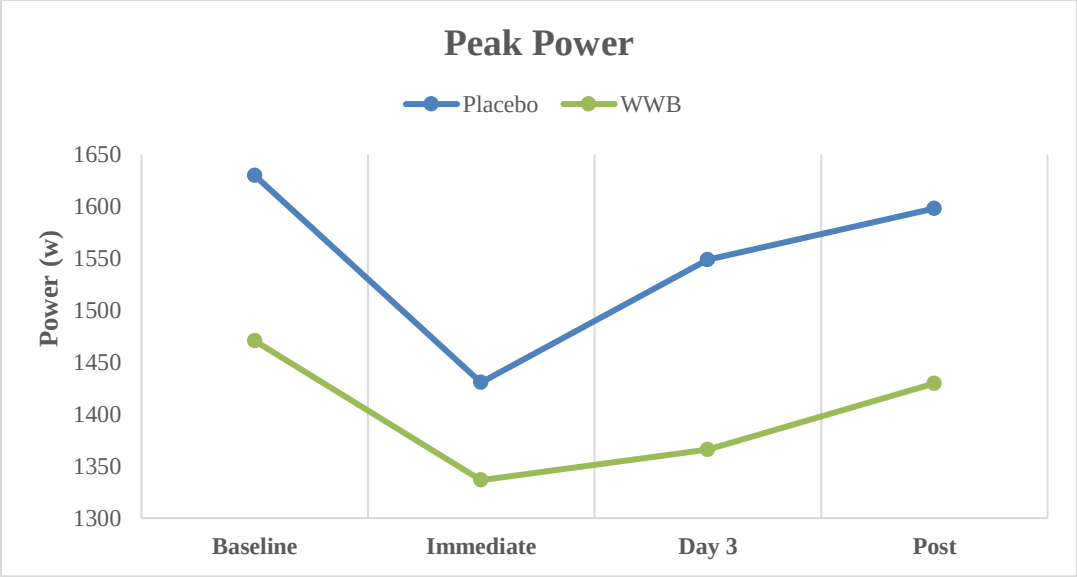

Figure 14. *Comparison of peak power for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups); W: Watts.*

4.5.4 Peak Velocity

The results revealed no significant peak velocity and condition interaction ($p > 0.05$). However, there was a significant main effect of time F (3, 66) = 21.660, $p < 0.001$ (Tables 6-7, Figure 15).

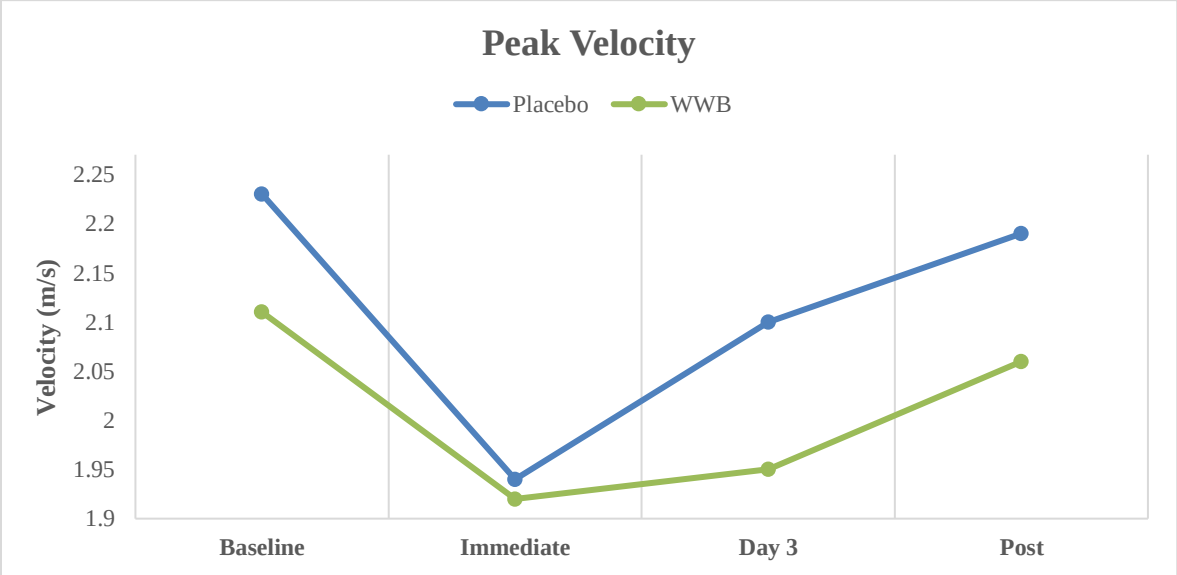

Figure 15. *Comparison of peak velocity for participants in both the WWB and placebo groups over time. *Significant main effects of Time (collapsed across groups); m/s: meters per second.*

Table 6. Athletic Performance Parameters Prior and After DOMS

Jump Height (cm) *		**Placebo**	**WWB**
Baseline[bc]	Mean	33.27 ± 8.07	34.01 ± 9.47
Immediate [acd]	Mean % diff pre	28.01 ± 11.48 -15.81%	27.06 ± 13.15 -20.44%
Day 3[ab]	Mean % diff pre	30.58 ± 7.45 -8.09%	31.43 ± 11.45 -7.59%
Post[b]	Mean % diff pre	32.33 ± 8.17 -2.83%	33.48 ± 2.99 -1.56%
Ground Contact Time (sec)*			
Baseline[b]	Mean	0.63 ± 0.18	0.68 ± 0.13
Immediate[acd]	Mean % diff pre	0.76 ± 0.23 20.63%	0.69 ± 0.17 1.47%
Day 3[b]	Mean % diff pre	0.63 ± 0.17	0.66 ± 0.17 -3.03%
Post[b]	Mean % diff pre	0.63 ± 0.13	0.65 ± 0.16 4.41%
Peak Velocity (m/s)*			
Baseline[bc]	Mean	2.23 ± .40	2.11 ± 0.36
Immediate[acd]	Mean % diff pre	1.94 ± 0.42 -13.00%	1.92 ± 0.50 -9.00%
Day 3[ab]	Mean % diff pre	2.19 ± 0.36 -1.79%	1.95 ± 0.45 -7.58%
Post[b]	Mean % diff pre	2.20 ± 0.42 -1.35%	2.06 ± 0.42 -2.37%
Peak Power (W)*			
Baseline[bc]	Mean	1629.93 ± 485.30	1470.70 ± 302.31
Immediate[acd]	Mean % diff pre	1430.50 ± 494.99 -12.24%	1336.50 ± 343.87 -9.12%
Day 3[abd]	Mean % diff pre	1548.79 ± 471.58 -4.98%	1365.80 ± 348.67 -7.13%
Post[bc]	Mean % diff pre	1598.21 ± 493.77 -1.95%	1429.40 ± 301.79 -2.81%

*Mean ± SD; * significant main effect of time (collapsed across groups) ($p < 0.05$); WWB: white willow bark; sec: seconds; W: watts; m/s: meters per second; cm: centimeters.*

a: a significant time difference from baseline
b:a significant time difference from immediate
c: a significant time difference from day 3
d: a significant time difference from post

Table 7. Effect Size (*d*) Between Days for Athletic Performance

	BL & IR	BL & D3	BL & Post	IR & D3	IR & Post	D3 & Post
JH	0.57	0.29	0.08	0.31	0.50	0.20
GCT	0.41	0.06	0.13	0.43	0.50	0.06
PP	0.37	0.27	0.06	0.10	0.30	0.21
PV	0.56	0.43	0.10	0.16	0.45	0.33

JH: jump height; GCT: ground contact time; PP: peak power; PV peak velocity; BL: baseline; IR: immediate response; D3: day 3.

CHAPTER V

DISCUSSION

To the best of our knowledge, this was the first investigation to examine the effects of white willow bark (WWB) on the parameters of DOMS. Pain, swelling, and loss of muscle function following eccentric exercise are the trademarks of inflammation (Smith, 1991). In the current investigation, when collapsed across groups, the significant decrease ($p < 0.05$) in vertical jump height, peak power, peak velocity, and increase in ground contact time and thigh circumference immediately following DOMS indicates inflammation had occurred (Fridén et al., 1983; Smith, 1991) The immediate changes following exercise verifies that the training protocol was effective in fatiguing the legs. The primary findings of this investigation demonstrate WWB may decrease subjective muscle soreness better than the placebo (Table 2; Figures 4-7). Moreover, WWB appears to blunt the decrease in pressure pain threshold that often accompanies muscle damage. While not significant ($p > 0.05$), the WWB group pressure pain threshold was higher than the placebo group 72hrs following the muscle damaging exercise protocol. The secondary findings of this investigation are inconclusive regarding the ability of WWB to promote a faster recovery of muscle function and the preservation of athletic performance. No difference ($p > 0.05$) was found between the treatment conditions for jump height, ground contact time, and peak velocity and peak power following the induction of DOMS (Tables 3; Figures 12-15).

Both groups resulted similar detrimental effects following DOMS on performance and were almost evenly matched on their rate of muscle recovery and improvements in performance during the investigation.

5.1 Muscle Soreness and Discomfort

While not significant ($p > 0.05$), the consumption of WWB following an exhaustive bout of resistance training may decrease subjective muscle soreness or pain greater than the placebo in healthy individuals (Table 2, Figures 4-7). It all time frames, except for day-five for the gastrocnemius muscle, the rating of muscle soreness or discomfort was lower than that of the placebo. During the peak (approximately 48hrs following exercise) of gluteal muscle soreness, the placebo group rating of muscle soreness or discomfort was 21.53% higher than that of the white willow bark (77.18 ± 17.82mm; 60.56 ± 26.88mm, respectively). In both groups, hamstring muscle soreness peaked within 24hrs of exercise and the placebo group was 28.35% more sore than those in the WWB group (44.80 ± 26.96mm; 32.10 ± 28.81mm respectively). Peak soreness for the quadriceps in both groups occurred on day three (72 hours) following resistance training. While not statistically significant, the WWB group rated their muscle soreness 22.53% lower than the placebo (53.40 ± 31.43mm; 68.93 ± 27.51mm respectively). Unexpectedly, following the five days of supplementation, the quadriceps muscle soreness remained elevated from baseline in both the WWB (pre: 0.10 ± 0.54mm; post: 7.50 ± 8.41mm) and the placebo (pre: 0.88 ± 1.17mm; post 9.02 ± 10.84mm) groups. This residual muscle soreness could be explained due to the quadriceps being the primary muscle activated during lunges and seated leg press. The trend of WWB being superior to placebo in decreasing subjective muscle soreness is in agreement with other studies that examined the effectiveness of willow bark on decreasing pain (Biegert, et al 2004; Churbasik et al 2000; Schmidt et al 2001). Biegert, et al (2004) found that willow bark decreased joint pain

more than the placebo after six weeks of treatment (15% vs. 4% respectively). Schmidt et al (2001) found after two weeks of consuming of 240mg salicin osteoarthritis pain was decreased by 14% while those in the placebo group had a 2% increase in pain. Churbaskik et al (2000) concluded that WWB with a salicin content ranging from 120mg-240mg provided significantly more pain reduction than placebo. However, caution should be warranted with interpreting the results since participants were allowed to take tramadol as a rescue medication.

5.2 Pressure Pain Threshold

Pressure pain threshold is believed to correlate with an individuals' perceived pain intensity (Fleckenstein et al., 2017). The results showed no significant ($p > 0.05$) difference between the groups on mid-thigh pressure pain threshold (Table 2, Figure 8-9). The WWB group pressure pain threshold was considerable higher than the placebo group 72hrs following resistance training. In the WWB group, 72hrs after exercise, both right and left mid-thigh pressure pain threshold was lower than what it was at baseline (3.05% and 3.69% respectively). In comparison, in the placebo group, right mid-thigh pressure pain threshold was 13.76% lower than baseline and the left mid-thigh 10.03% lower than baseline. When collapsed across groups, there was a significant ($p < 0.05$) time difference for right mid-thigh pressure pain threshold with day three (72hrs) following resistance training and significantly lower than day six (post). This is in agreement with results from an investigation by Fleckenstein et al (2017) that found pressure pain threshold was significantly lower at both 48 and 72 hours following DOMS. The decrease in pressure pain threshold may be due to the release of endogenous substances following muscle damage which desensitize muscle nociceptors mechanical stimulations (Mense, 2009) or an increase in mechanical sensitivity due to inflammation allowing high-threshold mechanosensitive receptors (HTM) to become susceptible to weaker stimuli (Diehl,1992). The data suggest that

willow bark shows a potential to maintain pressure pain threshold following exercise because those in the WWB group exhibited remarkably higher pressure pain threshold 72hrs following exercise.

5.3 Mid-Thigh Circumference

This is the first study to examine the effects of WWB on thigh circumference. Thigh circumference was used to measure the acute inflammatory response that occurs following DOMS. Assessing circumference is often used in research to measure the changes in inflammation over time (Manimmanakorn et al., 2016; Kazunori Nosaka & Clarkson, 1996; Tanabe et al., 2015). Measurements of thigh circumferences are an indicator of acute changes in the thigh volume due to inflammation associated with exercise induced muscle injury (Nosaka & Clarkson, 1995). In the current investigation, an increase in mid-thigh circumference developed quickly following the cessation of exercise and continued to stay elevated compared to baseline during the five days of supplementation. The immediate inflammatory response resulting in an increase in thigh circumference is consistent with other studies that examined acute responses of DOMS on parameters of muscle damage (Manimmanakorn et al., 2016; Kazunori Nosaka & Clarkson, 1996; Tanabe et al., 2015).

The results of this study found no significant ($p > 0.05$) difference between the two treatments (Table 3, Figures 10-11). However, further analysis revealed the immediate right and left mid-thigh circumference was significantly ($p < 0.05$) greater following resistance training when collapsed across groups. Peak thigh circumference occurred immediately following exercise and was significantly higher than the baseline value. In the WWB group, immediately following exercise, right mid-thigh circumference was 1.58% higher than baseline and the left mid-thigh was 1.68% higher than baseline. In comparison, in the placebo, both right and left mid-

thigh circumference increased following training (1.77% and 2.23% respectively). During this six day study, both groups showed a similar pattern of declining inflammation following training. Thigh circumference for both treatment conditions were similar across time. Due to no obvious differences between the two treatment conditions, the effect of WWB deceasing inflammation assessed by thigh circumference is inconclusive. Future studies should examine thigh circumference and markers of inflammation such as IL-6, IL-8 or IL-β to further investigate WWB effectiveness in decreasing inflammation.

5.4 Athletic Performance

This was the first investigation to examine the effects of WWB on the ability to maintain athletic performance following DOMS. Jump height provides an index of muscle power of the lower limbs (Nicol et al., 2015) and following a fatiguing exercise evaluates the recovery of the neuromuscular function. In this study, a four countermovement jump test was utilized. The results from this investigation revealed no significant ($p > 0.05$) differences between treatment groups in regards to jump height, ground contact time, peak velocity, or peak power following exercise (Table 4; figures 12-15). Further analysis revealed, when collapsed across groups, there was a significant ($p < 0.05$) main effect of time. The baseline jump height was significantly higher than both immediately and 72hrs (day three) following resistance training. In addition, ground contact time was significantly lower immediately following exercise compared to baseline, 72hrs (day three) and post supplementation (day six) regardless of condition.

As anticipated, the jump height measurement immediately following exercise confirmed that the participants' lower legs were fatigued. For WWB group, jump height decreased by 20.44% and ground contact time increased by 1.47%. The immediate response for the placebo group was similar in which jump height decreased by 15.81% with ground contact time

increasing by 20.63%. These results agree with other's (Bryane and Eston 2002; Caldwell et al., 2018) which showed that following eccentric exercise, jump height was significantly lower immediately following exercise. Following the five-day supplementation period, the placebo group's jump height was 2.83% lower than baseline and WWB was only 1.56% lower than baseline. Both groups had similar patterns of recovery regarding peak power and peak velocity with day six (post) measurement slightly lower than baseline. In fact, compared to baseline, the placebo group (peak velocity: -1.35%; peak power: -1.95%) showed a slightly better recovery than the WWB (peak velocity: -2.37%, peak power: -2.81%) on both variables. The conclusion on the ability of WWB to enhance muscle recovery following DOMS in inconclusive.

5.5 Conclusion

The purpose of this study was to compare the effects of WWB to a placebo on the parameters of DOMS following an exhaustive lower leg resistance training session. To the best of our knowledge, this is the first study to investigate the potential of WWB in decreasing both pain and inflammation following exercise in healthy adults. After the five-day supplementation period following the induction of DOMS, there were no significant difference between the treatment conditions on any variable. Despite not being statistically significant, WWB decreased subjective pain and soreness evaluated by the VAS and preserved pressure pain threshold more than the placebo. For all daily measurements during the five-day supplementation period, those in the WWB group rated their muscle discomfort lower than the placebo with a pronounced lower VAS rating for muscle soreness or discomfort 24-72hrs following exercise.

Using a VAS to rate individual soreness is shown to be reliable and is used in previous investigations regarding DOMS and pain (Hoseinzadeh et al., 2015; Pumpa et al., 2013; Wheeler & Jacobson, 2013). The subjective nature of these scales should be discussed. The ability to deal

with pain and discomfort will vary among individuals and may be influenced by their current and past training experiences. Dealing with pain or discomfort is reflected to the individuals' pain threshold and their ability to cope with both the mental and physical manifestations of pain (pain tolerance) (Pen et al., 1995). While there is no difference in pain threshold in athletes and no-athletes, athletes have a superior pain tolerance over non-athletes (Azevedo & Samulski, 2003). In addition, trained individuals are shown to have more control over the debilitating effects of muscle soreness compared to novice (Pen et al., 1995). While the exact mechanism leading to an athletes' superior pain tolerance is not known, it is suggested that both current and past athletes have developed superior cognitive coping strategies to redirect their focus (dissociation) or focus on the pain to reinterpret it (association)(Azevedo & Samulski, 2003; Pen et al., 1995). While none of the participants were actively taking part in a lower body resistance training program at the time of the study, their past training history may have had an influence on their perceived muscle soreness and discomfort. While their pain threshold was similar, those accustomed to the feeling of DOMS may have rated this perceived muscle soreness or discomfort as minimal compared to those with less experience of DOMS or with a lesser cognitive coping strategy.

The placebo effect may have influenced the ratings of subjective muscle discomfort or pain following DOMS. The placebo effect is a powerful phenomenal aspect that can influence the physiological mechanisms and outcomes of pain (Colloca, 2019). For instance, in a study by Levine and colleagues (1981) postoperative patients recovering from molar extractions received either saline (placebo) or 6-8mg of morphine. The results showed that both groups of patients experienced a similar degree of pain relief. In an investigation by Carvalho et al. (2016) patients suffering from chronic low back pain were given an open label placebo prescription to take with their treatment as usual. At the end of the three week study, those patients taking the label placebo prescription experienced significant ($p < 0.05$) pain relief and a decrease in back pain-related disability more than those who continued their treatment as usual only. The consumption

of a possible analgesic medication along with an expectation that the medication is going to provide relief can lead to an analgesic response (Rossettini et al., 2018). In comparison, the administration of an analgesic medication with no expectations of pain relief can lead to exacerbation of pain (Rossettini et al., 2018). In this investigation, 60% of participants regardless of group believed they had the WWB and 40% of the participants believed they had the placebo. When the data was broken down into individual treatment groups, 25% of those in the placebo believed they had the WWB and 36% in the WWB correctly guessed they had WWB. The participants belief that they were consuming WWB, regardless of grouping, may resulted in a lower pain rating due to their belief that the supplement or placebo was working. In addition, neutral stimulus such as the color, taste, or smell of the supplement could have led to the association of taking an analgesic and enhancing the pharmacological effect of the supplement (Colloca, 2019). Research has shown that white placebo pills are perceived as analgesics and large capsules are perceived to offer stronger pharmacological effects (Turner et al., 1994). In this investigation, the placebo pills contained powdered sugar in large capsules. The appearance of the placebo in this investigation could have led to the belief that they had the WWB and resulted in a perceived analgesic effect. Future investigations on the effect of WWB on DOMS should have a control that does not receive treatment to counteract any influences of a placebo effect.

Quadriceps muscle soreness peaked on day three (72 hrs.) following exercise. This correlated with the significant decrease in pressure pain threshold observed on day three for the right mid-thigh. The pressure pain threshold for day three in the placebo group was 5.20% and 10.03% lower than the baseline measurements for the right and left mid-thigh, respectively. WWB was able partially eliminate the detrimental effects that inflammation and muscle damage had on pressure pain threshold. The average pressure pain threshold in the WWB was 1.71% and 3.69% lower than baseline during the peak of muscle soreness for the right and left mid-thigh respectively. The results of the investigation revealed, while not statistically significant, WWB

was superior to the placebo in maintaining pressure pain threshold. Furthermore, the ability of WWB to decrease inflammation which was evaluated by thigh circumference remains inconclusive. Thigh circumference was significantly higher immediately following exercise compared to both baseline and post-supplementation (day six). Both groups showed similar patterns of declining inflammation during this investigation as DOMS resolved on its own. In addition, during the five days of supplementation, none of the participants reported any adverse events while taking the supplement. This may confirm that WWB is tolerated better than NSAIDs or aspirin. This is in agreement with other studies that concluded that WWB is tolerated with no or mild side effects (Saller et al., 2008; Uehleke et al., 2013).

There results of the investigation reveal that the ability of WWB to maintaining athletic performance following an exhaustive bout of exercise is inconclusive. Both the WWB and placebo showed similar trends in the peaking of deliberating effects and had similar rate of recovery following the induction of DOMS. Both groups had the largest decrease in jump height, peak power, and peak velocity and the longest ground-contact time immediately following exercise suggesting the participants' legs were fatigued. Unexpectedly, the placebo group showed a trend to being slightly superior to WWB in recovery of athletic performance. Perhaps, motivation played a greater role than skeletal muscle soreness and damage during the four counter-movement repeated jumps when participants were asked to give maximal effort. Taken together, our findings conclude that WWB may offer some analgesic effects following a bout of exhaustive exercise as observed by the lower VAS scores and increased pressure pain threshold compared to the placebo. However, the ability of WWB to enhance recovery from skeletal muscle damage following exhaustive exercise, improve athletic performance and its ability to decrease inflammation remains inconclusive.

There were limitations that need to be considered in the present study. The primary limitation of the current study was the small sample size. It is speculated that increasing the

sample size may have elicited significant differences between the groups regarding the subjective rating of muscle soreness or discomfort and the pressure pain threshold. In addition, measuring thigh circumference, pressure pain threshold and assessing athletic performance at both 24hrs and 48hrs following training may have revealed significant difference between the treatment conditions. A secondary limitation in the study is the lack of a control group. The placebo effect may have impacted the VAS scores and pressure pain threshold. The inclusion of a control group that did not take part in any treatment could bring more clarity on the analgesic effects of WWB by counteracting the placebo effect that may have occurred. The addition measuring inflammatory cytokines such as IL-6, IL-8, or TN-α can help determine the effects of WWB on inflammation in healthy adults. Future research will need to continue to study the analgesic and anti-inflammatory properties of WWB in non-clinical populations to determine if would be a successful alternative to aspirin or other NSAIDs.

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APPENDICES

APPENDIX A

Health History and Exercise Questionnaire

RECRUITMENT NO._____

HEALTH HISTORY AND EXERCISE QUESTIONNAIRE

OKLAHOMA STATE UNIVERSITY

DEPARTMENT OF HEALTH AND HUMAN PERFORMANCE

Name _____ Date_____

Work Phone _____ Home Phone (Cell) _____

E-mail address_____ Preferred method of contact: Call, email, or text

Person to contact in case of emergency_____

Emergency Contact Phone _____

Gender_____ Age _____(yrs) Height _____(ft)_____(in) Weight_____(lbs)

Does the above weight indicate: a gain____ a loss____ no change____ in the past year?
If a change, how many pounds?_____(lbs)

A. JOINT-MUSCLE STATUS (✓Check areas where you currently have problems)

Joint Areas	Muscle Areas
( ) Wrists	( ) Arms
( ) Elbows	( ) Shoulders
( ) Shoulders	( ) Chest
( ) Upper Spine & Neck	( ) Upper Back & Neck
( ) Lower Spine	( ) Abdominal Regions
( ) Hips	( ) Lower Back
( ) Knees	( ) Buttocks
( ) Ankles	( ) Thighs
( ) Feet	( ) Lower Leg
( ) Other_____	( ) Feet
	( ) Other_____

B. HEALTH STATUS (✓Check if you currently have any of the following conditions)

( ) High Blood Pressure	( ) Acute Infection
( ) Heart Disease or Dysfunction	( ) Diabetes or Blood Sugar Level Abnormality
( ) Peripheral Circulatory Disorder	( ) Anemia
( ) Lung Disease or Dysfunction	( ) Hernias
( ) Arthritis or Gout	( ) Thyroid Dysfunction
( ) Edema	( ) Pancreas Dysfunction
( ) Epilepsy	( ) Liver Dysfunction
( ) Multiply Sclerosis	( ) Kidney Dysfunction
( ) High Blood Cholesterol or Triglyceride Levels	( ) Phenylketonuria (PKU)
	( ) Loss of Consciousness
( ) Allergic Reactions to Rubbing Alcohol	( ) Allergic or Sensitive to Saliculates
( ) Hemophilia	( ) Stomach Ulcers
( ) Chronic Low Back Pain	( ) Chronic Knee Pain
( ) Asthma	( ) Gastritis

C. SURGICAL STATUS ((✔Check if you have had surgery involving the following in the past 12 months)

( ) Knee
( ) Ankle
( ) Back
( ) Hip

D. PHYSICAL EXAMINATION HISTORY

Approximate date of your last physical examination_____

Physical problems noted at that time_____

Has a physician ever made any recommendations relative to limiting your level of physical exertion? _____YES _____NO
If YES, what limitations were recommended?_____
_____

E. CURRENT MEDICATION (PRESCRIPTION OR OVER THE COUNTER) AND SUPPLEMENT USAGE (List the drug name and the condition being managed)

MEDICATION	CONDITION
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Are you currently taking any of the follow medications? Please circle **YES** or **NO** for the following questions.

Anti-coagulants (blood thinners)	YES	NO
Beta Blockers	YES	NO
Diuretics (water pills)	YES	NO
Methotrexate	YES	NO
Phenytoin (Dilantin)	YES	NO
Prescription NSAID	YES	NO
Corticosteroids	YES	NO

F. **FEMALES ONLY**: Please circle **YES** or **NO** for the following questions.

Are you pregnant? **Yes** **No** Are you currently breastfeeding? **Yes** **No**

G. **PHYSICAL PERCEPTIONS** (Indicate any unusual sensations or perceptions. ✓Check if you have recently experienced any of the following during or soon after *physical activity* (PA); or during *sedentary periods* (SED))

PA	SED		PA	SED	
( )	( )	Chest Pain	( )	( )	Nausea
( )	( )	Heart Palpitations	( )	( )	Light Headedness
( )	( )	Unusually Rapid Breathing	( )	( )	Loss of Consciousness
( )	( )	Overheating	( )	( )	Loss of Balance
( )	( )	Muscle Cramping	( )	( )	Loss of Coordination
( )	( )	Muscle Pain	( )	( )	Extreme Weakness
( )	( )	Joint Pain	( )	( )	Numbness
( )	( )	Other_____	( )	( )	Mental Confusion

H. **FAMILY HISTORY** (✓Check if any of your blood relatives . . . parents, brothers, sisters, aunts, uncles, and/or grandparents . . . have or had any of the following)

( ) Heart Disease
( ) Heart Attacks or Strokes (prior to age 50)
( ) Elevated Blood Cholesterol or Triglyceride Levels
( ) High Blood Pressure
( ) Diabetes
( ) Sudden Death (other than accidental)

I. **EXERCISE STATUS**

Do you regularly engage in aerobic forms of exercise (i.e., jogging, cycling, walking, etc.)? **YES** **NO**

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you regularly lift weights? **YES** **NO**

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you regularly play recreational sports (i.e., basketball, racquetball, volleyball, etc.)? **YES** **NO**

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you perform any lower body resistance exercises? **YES** **NO**

Do you perform any of these lower body resistance exercises on a regular basis? (✓Check if you currently perform any of these lower body resistance exercises)

Leg Extension ( ) Leg Press ( )

Squats ( ) Lunges ( )

Hamstring Curls ( ) Dead Lift ( )

Appendix B

Visual Analog Scale

Each **morning (when you wake)** place a mark **X** on the line to indicate your discomfort.

Day 1

Calf None ---------- Extreme

Quads None ---------- Extreme

Hamstring None ---------- Extreme

Buttock None ---------- Extreme

Day 2

Calf None ---------- Extreme

Quads None ---------- Extreme

Hamstring None ---------- Extreme

Buttock None ---------- Extreme

Day 3

Calf None ---------- Extreme

Quads None ---------- Extreme

Hamstring None ---------- Extreme

Buttock None ---------- Extreme

Day 4

Calf None ---------- Extreme

Quads None ---------- Extreme

Hamstring None ---------- Extreme

Buttock None ---------- Extreme

Day 5

Calf None ---------- Extreme

Quads None ---------- Extreme

Hamstring None ---------- Extreme

Buttock None ---------- Extreme

APPENDIX C

IRB Approved Informed Consent for Participation

Applied Exercise Science

The Effect of White Willow Bark on Delayed Onset Muscle Soreness

Background Information

You are invited to be in a research study of the effects of the supplement White Willow Bark in the alleviation of common muscle soreness following a workout. We ask that you read this form and ask any questions you may have before agreeing to be in the study. Your participation in this research is entirely voluntary. There is not penalty for refusal to participate, and you are free to withdraw your consent and participation in this project at anytime. Your decision whether or not to participate in this study will not affect your grade in any class.

This study is being conducted by: Brandie Cheshier under the direction of Dr. Bert Jacobson, both of School of Kinesiology, Applied Health and Recreation at OSU.

Procedures

If you agree to be in this study, we would ask you to do the following things:

1. Initially, you will report to the Neuromuscular Physiology lab (session 1) to sign the informed consent and fill out the health history questionnaire. You will become familiar with the procedures of the vertical jump and practice a few jumps to make sure you are comfortable with the procedures. In addition, your weight and height will be measured for a body mass index calculation.

2. On your scheduled day (session 2), you will report to Neuromuscular Physiology lab. First, you will rate your initial muscle soreness on the visual analog scale. Then your right and left thigh circumference will be measure at the belly of your quadriceps.

3. Following thigh circumference, a pressure algometer will used to provide pressure to induce tenderness or pain on your right and left thigh. Then you will be assessed on the vertical jump.

4. At the Colvin Recreation Center, you will perform lower body exercise to induce skeletal muscle fatigue. Exercises will include:
    a. 5X10 lunges (60% body weight)
    b. 3X10 leg press (75% body weight)

5. Immediately following exercise you will go back to the Neuromuscular Physiology lab and sit for 10-15 minutes. Then you will have another measurement of thigh circumference. In addition, the amount of pressure required to induce pain/tenderness assessed again. Then you will perform one more vertical jump. Finally, you will be given an oral supplement (2 capsules) White Willow Bark or a placebo with 1/3 of a protein bar.

6. You will then be asked to continue supplement/placebo dosing for the next 5 days with food in the morning, noon, and at night. In addition you will rate you soreness on a visual analog scale as soon as you wake for the next 5 days. During this time, you will be asked to refrain from participating in any lower body exercise to not interfere with the current study.

7. On day 3 (session 3), you will report back to the Neuromuscular Physiology lab where you will again perform the vertical jump test, have a measurement of your thigh circumference and the amount of pressure to induce pain/tenderness assessed again.

8. On day 6 (session 4), you will report back to the Neuromuscular Physiology lab at your scheduled time to return your visual analog scale and have a final measurement of thigh circumference, the amount of pressure to induce pain/tenderness assessed for the last time, and perform the final vertical jump test.

Approved:
Protocol #: IRB-20-44

Participation in the study involves the following time commitment: The total time commitment in the Neuromuscular Physiology lab for session 1 is 30 minutes. Session 2 which takes place in the Neuromuscular Physiology Lab and Colvin Recreation Center, the total time commitment is about 60 minutes. Day 3 (session 3) and Day 6 (session 4) time commitment at the Neuromuscular Physiology lab for vertical jump test, thigh circumference, and pressure to induce pain/tenderness is about 15-20 minutes each.

Risks and Benefits of being in the Study

The study involves the following foreseeable risks:
The risk associated with the oral consumption of the supplement White Willow Bark is mild and similar to that of the over the counter medications that contain salicylates such as Aspirin. The risks of all compounds containing salicylates include: stomach upset, nausea, ulcers, stomach bleeding. In order to assist with offset of these risk, you are instructed to take the supplement with food. In case of injury or illness resulting from this study, emergency medical treatment will be available at University Health Services on the OSU Stillwater Campus. No funds have been set aside by Oklahoma State University to compensate you in the event of illness or injury
The benefits to participation are:
There are no direct benefits to you. More broadly, this study may help the researchers learn more about White Willow Bark and may help determine if White Willow Bark is effective in decreasing skeletal muscle soreness following exercise.

Reduce the Risk of COVID-19

Screening: Researchers and participants who show potential symptoms of COVID-19 (fever, cough, shortness of breath, etc.) will **NOT** participate in this study at this time. In addition, before any scheduled sessions both the researchers and participants must self-screen for COVID-19. If any participant is suspected of having or been exposed to COVID-19 during the duration of this study they will not be allowed to further participate in the study until they have tested negative for COVID-19.

Physical distancing: Whenever possible, we will maintain at least 6 feet of distance between persons while conducting the study.

Mask/Covering: Researchers and participants will be required to shield their mouth and nose with a cloth face cover or mask during the study, even when maintaining at least 6 feet of distance. Only during the fatiguing protocol will the participants not be required to wear their face covering. Tissues will be available to cover coughs and sneezes.

Gloves: When the researchers has direct contact with the participant (thigh circumference and using the pressure algometer to provide pressure to induce tenderness or pain) the research will wear latex free-gloves to further reduce the risk of COVID-19 exposure.

Handwashing: Researchers and participants will wash hands or use a hand sanitizer containing at least 60% alcohol before all testing procedures.

Disinfecting materials: When feasible, researchers will clean and disinfect surfaces between participants, using an EPA-registered disinfectant or a bleach solution (5 tablespoons of regular bleach per gallon of water) for hard materials and by laundering soft materials. Disinfected materials will be handled using gloves, paper towel, plastic wrap or storage bags to reduce the chance of re-contamination of materials.

Electronics: Alcohol-based wipes or sprays containing at least 70% alcohol will be used to disinfect shared touch screens, mice, keyboards, etc. Surfaces will be dried to avoid pooling of liquids.

Compensation

You will receive no payment for participation in this this study.

Confidentiality

Only qualified research personnel and the Oklahoma State University Institutional Review Board (IRB) will have access to the database containing study information (P.I., and the advisor of the P.I). You information will be stored

on the primary investigator's computer that is not accessible to anyone other than the primary investigator. The signed consent forms will be kept for 3 years per federal guidelines. Once your demographic data is obtained from the medical questionnaire (height, weight, gender, and age) and put onto an excel document, your medical history questionnaire will be shredded. All data collected (visual analog scale scores, height, weight, gender, and age) will be saved on the hard drive of the PI's work computer. All data collected will be reported as groupings (position) and will not be linked to participants. The researchers will not be able to remove your data from the dataset once your participation is complete. The Seretean Wellness Center can be accessed by the public, but the room that contains all documents remains locked on a regular basis and can only be accessed by the PI.

The list of corresponding names and ID numbers will be stored in a locked desk in the PI's office. The data will be stored on a hard drive that will be locked in the Primary investigators office. The hard drive will only be accessible while the PI is at work, and will only be used while he or she is at work. To elaborate, your medical questionnaire will be destroyed immediately after your demographic data input has been recorded and saved onto the PI's office computer. For example, if subject M1 comes in on a Monday, shortly after he finishes his initial assessment procedures, meets all inclusion criteria, and all data is saved on the PI's computer (the same day), his health data will be shredded. In addition, all information that pertains to the individuals who do not meet inclusion criteria will also be shredded immediately.

It is important to note that the data collected during this research study may be shared with other researchers in the future. If this happens, no identifiable information will be shared. It is unlikely, but possible, that others responsible for research oversight may require us to share the information you give us from the study to ensure that the research was conducted safely and appropriately. We will only share your information if law or policy requires us to do so. Finally, confidentiality could be broken if materials from this study were subpoenaed by a court of law.

Contacts and Questions

The Institutional Review Board (IRB) for the protection of human research participants at Oklahoma State University has reviewed and approved this study. If you have questions about the research study itself, please contact Brandie Cheshier at (214) 801-0236, brandie.cheshier@okstate.edu or Dr. Bert Jacobson at (405) 744-933, bert.jacobson@okstate.edu. If you have questions about your rights as a research volunteer or would simply like to speak with someone other than the research team about concerns regarding this study, please contact the IRB at (405) 744-3377 or irb@okstate.edu. All reports or correspondence will be kept confidential.

Statement of Consent

I have read the above information. I have had the opportunity to ask questions and have my questions answered. I consent to participate in the study.

Signature:_____ Date: _____

Signature of Investigator:_____ Date: _____

Approved:
Protocol #: IRB-20-44

VITA

Brandie Cheshier

Candidate for the Degree of

Doctor of Philosophy

Dissertation: THE EFFECT OF WHTE WILLOW BARK ON DELAYED ONSET MUSCLE SORENESS

Major Field: Health, Leisure, and Human Performance

Biographical:

Education:

Completed the requirements for the Doctor of Philosophy in Health, Leisure, and Human Performance at Oklahoma State University, Stillwater, Oklahoma in May, 2021.

Completed the requirements for the Master of Science in Exercise Science at Texas Tech University, Lubbock, Texas in 2015.

Completed the requirements for the Bachelor of Science in Kinesiology at Texas Woman's University, Denton, Texas in 2010.

Experience:

Graduate Teaching Associate, August 2020-Present
School of Kinesiology, Applied Health, and Recreation
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Graduate Assistant, January 2018-Present
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