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American Ginseng Supplementation Does Not Attenuate Indices of Exercise Induced Muscle Damage

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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American Ginseng Supplementation Does Not Attenuate Indices of Exercise-Induced Muscle Damage

(Thesis format: Monograph)

By

Brent E. Smith

Graduate Program in Kinesiology

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

The School of Graduate and Postdoctoral Studies

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ABSTRACT

PURPOSE: To investigate the effect of American ginseng consumption on changes in average peak torque measures of dominant leg extensors following a downhill running bout.

METHODS: Ten university aged male volunteers were divided equally into two groups in this double-blind study. Both groups performed baseline tests to determine average peak torque of leg extensors. Subjects then began a 4 week supplementation period of American ginseng or placebo. They then performed a downhill treadmill run at a speed between 9.7-11.3 km/h and -12% grade. The muscle strength protocol involving the dominant leg extensors was then repeated at one, two, and three days following the downhill run. RESULTS: There was no group by time interaction effect for the isometric (p=0.182), isokinetic at 60 d/s (p=0.542), nor the isokinetic at 180 d/s (p=0.893). CONCLUSION: 4 weeks of American ginseng consumption prior to downhill running was unable to attenuate post-exercise reductions in muscle strength.

Key words: Muscle damage, eccentric, downhill running, ginseng,
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iii
TABLE OF CONTENTS

Abstract..........................................................................................................................ii

Acknowledgements........................................................................................................iii

Table of Contents...........................................................................................................iv

List of Tables..................................................................................................................viii

List of Figures................................................................................................................ix

List of Appendices..........................................................................................................x

Chapter 1 Introduction....................................................................................................1

Chapter 2 Review of Literature.......................................................................................6

  2.1 Brief History of Ginseng.........................................................................................7

  2.2 Types of Ginseng...................................................................................................8

  2.3 Aqueous and Alcohol Extracts of Ginseng...........................................................12

  2.4 Ginsenosides.......................................................................................................13
3.6 Maximal Oxygen Uptake..........................................................................................37

3.7 Food Record.........................................................................................................38

3.8 Ginseng and Placebo Capsules...........................................................................38

Chapter 4 Results.....................................................................................................40

4.1 Participant Data...................................................................................................41

4.2 Self Ratings of Muscle Soreness..........................................................................41

4.3 Isometric Contractions........................................................................................43

4.4 Isokinetic Contractions at 60 Degrees/Second......................................................44

4.5 Isokinetic Contractions at 180 Degrees/Second....................................................46

Chapter 5 Discussion...............................................................................................48

5.1 Overview and Major Findings..............................................................................49

5.2 Limitations..........................................................................................................50
LIST OF TABLES

Table 1- Physical Characteristics of Participants..........................................................41
LIST OF FIGURES

Figure 1- Core Chemical Structure of Four Groups of Ginsenosdies from Ginseng…………….15

Figure 2- Self Ratings of Muscle Soreness………………………………………………………42

Figure 3- Absolute Values of Isometric Peak Torque…………………………………………44

Figure 4- Absolute Values of Isokinetic Peak Torque at 60 Degrees/Second……………….45

Figure 5- Absolute Values of Isokinetic Peak Torque at 180 Degrees/Second……………….47
# LIST OF APPENDICIES

<table>
<thead>
<tr>
<th>APPENDIX</th>
<th>DESCRIPTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Participant Information Questionnaire</td>
<td>84</td>
</tr>
<tr>
<td>B</td>
<td>Par-Q &amp; You Questionnaire</td>
<td>86</td>
</tr>
<tr>
<td>C</td>
<td>Ginseng and Exercise Poster</td>
<td>87</td>
</tr>
<tr>
<td>D</td>
<td>Participant Food Records</td>
<td>89</td>
</tr>
<tr>
<td>E</td>
<td>Certificate of Approval of Human Ethics</td>
<td>90</td>
</tr>
<tr>
<td>F</td>
<td>Letter of Information</td>
<td>91</td>
</tr>
<tr>
<td>G</td>
<td>Letter of Informed Consent</td>
<td>97</td>
</tr>
</tbody>
</table>
CHAPTER 1- INTRODUCTION
Ginseng is part of the plant family Araliaceae and its species in the genus Panax (Helms. 2004; Bames et al. 2004). The name ginseng is derived from the Chinese words “Jen Sheng”, meaning “man-herb,” because the root or rhizome of the plant (the part of the plant most often consumed) has a humanoid shape (Lü et al. 2009). Furthermore, the name Panax means “all healing,” which portrays the traditional belief that ginseng has the ability to act as a “cure all” for all aspects of the body (Lü et al. 2009). Currently, ginseng is one of the best-selling medicinal plants in the world (Yun. 2001).

In Asian countries, ginseng root has been used for thousands of years in the traditional medicine system (Ang-Lee et al. 2001; Attele et al. 1999; Wang and Yuan. 2008) to benefit health and treat illness (Bensky et al. 1993). Ginseng, has been used as a tonic, prophylactic and/or ‘restorative’ agent (Goldstein. 1975; Hu. 1977; Liu and Xiao. 1992). According to Western botanical medicine texts from the 1800s and early 1900s, ginseng acts as both a mild sedative and stimulant useful for nerves and exhaustion, is used to increase circulation, and to treat dyspepsia (upset stomach or indigestion) (King. 1878; Ellingwood. 1915). Also, ginseng has been used to treat nervous disorders, anemia, wakefulness, shortness of breath, excess perspiration, forgetfulness, continuous thirst, lack of sexual desire, acute and chronic fatigue, and angina (Brekhman and Dardymov. 1969; Cartwright. 1979; Hu. 1976; Li and Li; 1973; Perry and Metzger. 1980). Furthermore, ginseng has been ingested as a preventative measure to protect against the effects of aging, fatigue, headaches, amnesia, tuberculosis, diabetes mellitus, and illnesses of the liver, heart and kidneys, (Baranov. 1966; Bittles et al.1979; Popov and Goldwag. 1973). Ginseng has also even been given to improve job-related efficiency involving physical labour (Perry and Metzger. 1980).
The most common forms of ginseng are Asian ginseng (Panax ginseng C.A. Meyer, named for Russian scientist Carl Anton Meyer in 1843 [Yun. 2001]) and American ginseng, which is also known as Panax quinquefolius L. (Lü et al. 2009). Asian ginseng is widely used and has been studied extensively (Ang-Lee et al. 2001; Yun. 2001) but the literature on American ginseng is rather limited (Yuan et al. 2004).

In the USA, ginseng is among the most regularly purchased herbs (Blumenthal. 2002). In fact, in 2002, a national survey of men and women concluded that 4-5% of people between the ages of 45-64 years consumed ginseng (Kaufman et al. 2002). Further, two Canadian surveys found that 17-32% of patients with cardiovascular disease used herbs and 6% of the people who were using herbs consumed ginseng (Pharand et al. 2003; Wood et al. 2003).

As the names suggest, Asian ginseng is grown in China, Korea, Japan, and Russia primarily (Helms. 2004) but also in Germany (Yun. 2001). American ginseng is native to North America (Borchers et al. 2000) but due to its popularity is cultivated worldwide (Li and Mazza. 1999). According to Agriculture and Agri-Food Canada, Canada is the world’s largest producer of American ginseng with Simcoe, Ontario accounting for much of Canada’s production with the rest being grown primarily in British Columbia. The other primary growing areas for American ginseng include Wisconsin in the United States as well as the northeast and northern areas of China (Agriculture and Agri-Food Canada).

Recent data suggest that American ginseng, similar to its Asian relative, has a variety of pharmacological actions (Qi et al. 2011). Antioxidant, anti-inflammatory, and immune-stimulatory activities are often suggested as the potential mechanisms responsible for the effects of ginseng (Qi et al. 2011). Specifically, American ginseng has been reported to have beneficial effects on the central nervous, cardiovascular, endocrine, and immune systems, and even to play
a role in cancer prevention (Court. 2000; Jin et al. 2010; Li et al. 2010a; Yuan and Dey. 2001) perhaps by inhibiting tumour cell growth (Qi et al. 2010b, Wang et al. 2007a, Wang et al. 2009b). Apparently, the ginsenosides (or ginseng saponins) are the major pharmacologically active ingredients in ginseng, promoting most of its actions including vasorelaxation, antioxidation, anti-inflammation and anti-cancer effects (Lü et al. 2009).

The ginsenoside profile that American ginseng possesses differs from that of its Asian relative in terms of the total number of ginsenosides, the ratio of protopanaxadiol (PPD) to protopanaxatriol (PPT), and other marker ginsenosides (Qi et al. 2011). In fact, the ginsenoside content in American ginseng is greater than other species of ginseng including Asian ginseng (Dharmananda. 2002). It has been suggested that the large variability in the ginsenoside content amongst different species and batches may play a role in the equally high variability in efficacy observed (Vuksan and Sievenpiper. 2005). Reports regarding the effectiveness of ginseng often contradict one another and this may be due to the differing chemical composition of ginseng root or root extracts, the method of extraction, subsequent handling, or even the season of its collection (Qi et al. 2011). For instance, when five batches of Ontario-grown American ginseng from five different farms were tested to evaluate their ability to reduce to reduce postprandial glycemia in healthy individuals, 60% the batches were able to exert glucose-lowering effects, yet 40% of did not reduce glucose to the degree that was anticipated. (Dascalu et al. 2007).

Nevertheless, American ginseng with a similar makeup could have similar physiological effects (Qi et al. 2011). Consequently, one could speculate that any two ginseng batches of similar profiles could produce similar efficacy.

In addition to these numerous reported benefits, there are also data that have shown supplementation with American ginseng in humans to be effective in attenuate circulating
creatine kinase, a marker of muscle damage, both during and at various time points following a bout of aerobic exercise (Hsu et al. 2005). Similarly, Asian ginseng can reduce plasma creatine kinase concentration following an aerobic exercise session (Jung et al. 2011). This suggests that ginseng (both American and Asian) might be useful as a recovery agent following exercise, since they may be able to attenuate exercise induced muscle damage, which in turn, could allow athletes to tolerate a greater training load, which may result in improved exercise performance. Nevertheless, the human data that exist on American ginseng and its relationship to post-exercise muscle damage attenuation is rather limited. Thus, there is the opportunity to explore this area of research and to formulate new ideas and knowledge pertaining to this topic. The aim of this thesis was to assess the effects of American ginseng on muscle damage using a more definitive outcome measure (muscle strength) that has not been used extensively in past ginseng studies.
CHAPTER 2- REVIEW OF LITERATURE
Much has been written about ginseng. As mentioned earlier, ginseng has an extensive history and is today one of the most commonly used medicinal plants worldwide (Qi et al. 2011). It has been reported to exert many beneficial physiological effects including vasorelaxation, antioxidation, anti-inflammation and anti-cancer (Lü et al. 2009). Some recent research has used purified individual ginsenosides to uncover the mechanism of action of ginseng as opposed to using ground up ginseng root which is far more typical (Buetnner et al. 2006; Gillis. 1997; Hofseth and Wargovich. 2007; Attele et al. 1999; Zhou et al. 2004; Cheng et al. 2005). This may be critical because it has been suggested that each individual ginsenoside has different pharmacologic effects due to its dissimilar structure (Lü et al. 2009).

One area of ginseng research that is rather limited is the effect of ginseng ingestion (especially American ginseng) on exercise-induced skeletal muscle damage in humans. This chapter reviews the ginseng literature in detail, including a brief synopsis of its history, the different varieties of ginseng, the various ginsenosides, (the major pharmacologically active ingredients in ginseng), and the link between ginseng and exercise-induced muscle damage. In addition, because muscle damage is a major component of this study, an overview of the literature on exercise-induced damage is also provided. Finally, information is presented on certain nutritional supplements and their ability to limit muscle damage, the repeated bout effect (prolonged protective effect of a single bout of eccentric exercise), and the methodology used typically to assess muscle damage.

2.1 Brief History of Ginseng

As mentioned, ginseng has an extensive history related to a wide variety of physical ailments. The origin of ginseng dates back to prehistoric times (Yun. 2001). In China, Shennong (Divine Peasant), who was also known as the Emperor Yan, the Yellow Emperor, or one of the
“Three Emperors,” was reported to have tasted a large number of plants resulting in the discovery of several medicinal herbs (Zheng. 1985). Dates of the original work are unclear but studies conducted by Shennong passed down by way of mouth over generations were amassed into a book entitled, “Shennong Bencao Jing (Shennong’s Herbal)” by Tao Hongjing during the Liang Dynasty, 502-557 AD (Wang. 1987). Apparently, there are 365 types of herb listed, separated into three categories based on their degree of toxicity (Yun. 2001). The best ones are non-toxic and reportedly can bolster vital energy when used consistently (Yun. 2001). Radix ginseng (a derivative of Asian ginseng), was an example of one of these “superior” herbs (Yun. 2001). Moreover, ginseng was mentioned by Chinese native, Shi You, in a piece of literature entitled, “Jizuyang (Interpretation of Creatures)” between 48 and 33 BC and prescriptions for ginseng can be found in “Shanghan Lun (Treatise on Fevers)” between the years 196 and 200 AD (Yun. 2001).

Today, ginseng is very popular and it is cultivated in various places throughout the world. In 1999, it was reported that over 3000 hectares are cultivated in Canada, primarily in Ontario and British Columbia (Li and Mazza. 1999). Ginseng can be purchased over the counter without a prescription and ginseng products are available commercially in a variety of forms, such as, roots, tablets and capsules, liquid extracts, and even in carbonated drinks and teas (Jia and Zhao. 2009).

2.2 Types of Ginseng

At least thirteen species of ginseng exist including: Panax japonicas (Japanese ginseng), cultivated in Japan, Panax major Ting, Panax notoginseng (Burkill) F.H. Chen (Sanchi ginseng), grown in China’s Yunnan province, Panax omeiensis J Wen, Panax pseudoginseng Wallich, found in Nepal and the eastern Himalayas, Panax sinesis J Wen, Panax stipuleanatus H. T. Tsai
& K.M. Feng, Panax trifolius L. (Dwarf ginseng), from Nova Scotia to Wisconsin and further south, Panax wanianus Sun, Panax zingiberensis C.Y. Wu & K.M. Feng, Panax vietnamensis Ha et Grushv (Vietnamese ginseng), Panax quinquefolius L. (American ginseng), and Panax ginseng C.A. Meyer (Yun. 2001). Panax quinquefolius L. is also called North American ginseng (Qi et al. 2011) and likewise, Panax ginseng C.A. Meyer is also called Asian, Korean or Chinese ginseng (Qi et al. 2011). Although Asian ginseng may refer to any ginseng grown in an Asian country (Yun. 2001), for the purposes of this thesis, when Asian ginseng is mentioned it means Panax ginseng C.A. Meyer.

There is also Siberian or Russian ginseng and while some claim that it has similar effects to other ginseng products, it is not derived from the Panax genus (Donovan et al. 2003) and is instead a totally different plant called Eleutherococcus senticosus (Baranov. 1982; Brekhman. 1965). Thus, it is not considered a “true” ginseng (Donovan et al. 2003) even though it is derived from the same family (Araliaceae) as American, Asian and other “true” ginsengs (Davydov and Krikorian. 2000). Although Siberian ginseng does not contain any ginsenosides (Brekhman. 1965; Cui et al. 1995), it does contain eleutherosides (Elyakov et al. 1964) and other chemical components that have been reported to induce some beneficial pharmacological actions (Davydov and Krikorian. 2000). However, the eleutherosides have a chemical structure that is entirely different from the ginsenosides (Bahrke and Morgan. 2000). Several of the reported physiological actions of Siberian ginseng, sometimes used as a less expensive alternative to Panax ginseng C.A. Meyer in the former Soviet Union and other countries as well (Bahrke and Morgan. 2000), are similar to that of “true” ginseng from the Panax genus such as, anti-cancer and immunostimulatory effects as well as anti-inflammatory and antioxidant effects (Davydov and Krikorian. 2000).
Unlike Siberian ginseng, Panax japonicus C.A. Meyer, also known as Japanese ginseng, is considered a “true” ginseng as it belongs to the Panax genus and thus, contains ginsenosides (Bahrke and Morgan. 2000). It is cultivated in Japan mainly, but also in India and Southern China (Phillipson and Anderson. 1984; Court. 1975; Williams. 1957). In Japan, it also has been used as an alternative to Panax ginseng C.A. Meyer to treat gastrointestinal disorders and also as an antitussive, expectorant and antipyretic (Bahrke and Morgan. 2000).

Panax ginseng C.A. Meyer or Asian ginseng was originally called Panax schinseng Nees in 1833 after the German botanist Nees van Esenbeck (Yun. 2001). Later, in 1843, it was renamed Panax ginseng C.A. Meyer after the Russian scientist Carl Anton Meyer (Yun. 2001). The production of Asian ginseng dates back to around 11 BC in Korea by transplantation of wild ginseng (Yun. 2001). Asian ginseng grown in Korea is said to be harvested following four to six years of cultivation and subsequently categorized into three forms depending on how it is processed (Yun. 2001). The three forms are fresh ginseng, harvested when it is less than four years old and consumed fresh, white ginseng, harvested when it is between four to six years old and then dried after being peeled, and red ginseng, harvested when it is six years old and then subsequently steamed and dried (Yun. 2001). Additionally, sun ginseng, which is white ginseng that has been steamed at 120 degrees Celsius (Kasai et al. 1983; Kwon et al. 2001), is sometimes considered to be another form of Panax ginseng that exhibit more powerful pharmacological effects, including vasorelaxation, antioxidant, and antitumor activities when compared to standard white or red ginseng (Keum et al. 2000; Kim et al. 2000).

In the traditional Chinese system of medicine, red ginseng has been utilized to help remedy physical ailments such as weak constitution, ulcers, cold symptoms, anemia as well as an analeptic (central nervous system stimulant), a stomachic (improves appetite and digestion) and
an erythropoietic (Matsuda et al. 1986). Importantly, extracts of red and white ginseng possess different ginsenosides (Chong and Oberholzer. 1988). To ensure high quality ginseng, the plant needs to be harvested in the fall season and never before five or six years of growth (Popov and Goldwag. 1973). For instance, ginseng roots may yield four ginsenosides initially, following five or six years of cultivation, they may yield up to nine ginsenosides (Liberti and Der Marderosian. 1978). However there is some debate because in Japan, it is believed the ginsenoside content in Asian ginseng nears maximum in the late summer following four years of cultivation (Soldati and Tanaka. 1984). Asian ginseng, the most widely recognized and researched form of ginseng, has been shown to induce a variety of beneficial physiological effects on health and well-being.

Like Asian ginseng, American ginseng (Panax quinquefolius L.) is another widely recognized type of ginseng, but it is not as well studied as its Asian relative (Yuan et al. 2004). It was discovered in 1716 near Montreal, Quebec (Evans. 1985) and has been utilized since as an energy booster and/or to achieve a sense of well-being (Li. 1995). It is advertised to have adaptogenic (an adaptogen is something that helps the body counteract stress and attain homeostasis) properties and has been used as an analeptic, tonic, stomach pain analgesic, and even as an aphrodisiac (Liberti and Der Marderosian. 1978).

There are three types of American ginseng available: cultivated, simulated wild and wild (Yuan et al. 2010). Most of the wild American ginseng flourishes in the upland, north- and east-facing woods because it is there where shade and loam soils are located (Yuan et al. 2010). Interestingly, American ginseng has now begun to be grown in some Asian countries, such as China (Yuan et al. 2010).
2.3 Aqueous and Alcohol Extracts of Ginseng

Although alcohol and aqueous extraction processes are available resulting in differing gensenoside content, often ginseng is ingested as ginseng root powder. Interestingly, a study using male Wistar rats found that while both aqueous and alcohol extracts of American ginseng attenuated rises in blood creatine kinase, only the aqueous extract was able to reduce morphological signs of damage and inflammation (Estaki and Noble. 2012). The prevention of rises in blood creatine kinase was thought to be due to the ginsenosides and their ability to enhance sarcolemma stability thus, preventing a disturbance to the membrane. Moreover, it was speculated that polysaccharides that are only found in the aqueous extract possess immunosuppressant characteristics and are able to limit the over activation of white blood cells, which may have explained the superior ability of the aqueous extract to protect against muscle damage when compared to the alcohol extract of American ginseng. (Estaki and Noble. 2012).

Furthermore a previous study in humans showed that American ginseng supplementation was able to attenuate rises in plasma creatine kinase induced by an exhaustive running protocol when the subjects consumed, what appears to be an aqueous extract evidenced by the phrase, “the Panax bearing ginsenosides content was determined from its degree of concentration in a hot water extract” (Hsu et al. 2005).

A study conducted by Azike et al. (2011), described the preparation of aqueous and alcohol extracts of ginseng. They mentioned how samples were ground and used to produce either the aqueous or alcohol extract and that the ginseng roots were soaked three times during a five hour period in 16 litres of water or an ethanol/water solution at 40 degrees Celsius. After the extraction, the solution underwent filtration at room temperature and the excess solvent was removed via a rotary evaporator under vacuum at 45 degrees Celsius. After the concentration
process was completed, the concentrates were freeze-dried at -50 degrees Celsius to produce the aqueous or alcohol ginseng in powdered form. Later analysis revealed that the alcohol and aqueous extract contained 28.25% and 13.87% of dry weight of extract respectively (Azike et al. 2011). Typically, the percent ginsenoside yield in ginsengs available for purchase is in the single digits. Originally, the plan for the present study was to study the aqueous extract used by Estaki and Noble (2012); however, this was not possible as it has not be approved for human use. Consequently, powdered American ginseng root grown in Canada that had not undergone any extraction procedure was obtained commercially (American Ginseng Vegi Capsules from Rootalive) and used in the present thesis. Its total ginsenoside content was 5.53% but, despite repeated requests to the manufacturer, the individual ginsenosides it contained was not available.

2.4 Ginsenosides

The majority of the beneficial physiological effects of ginseng, such as vasorelaxation, anti-oxidation, anti-inflammation and anti-cancer, have been attributed to its ginsenosides, the major pharmacologically active ingredients in ginseng (Lü et al. 2009). The ginseng root has been shown to hold 2-3% ginsenosides including Rg1, Rc, Rd, Re, Rb1, Rb2, and Rb0 (Lü et al. 2009). In excess of 40 ginsenosides or ginseng saponins have been identified and subsequently isolated from the root of Panax ginseng (Cheng et al. 2005; Nah. 1997). American ginseng has a greater ginsenoside content as more than 60 ginsenosides have been identified from various parts of Panax quinquefolius L., including the roots, leaves, stems, flower buds and berries (Christensen, 2009; Jia and Zhao. 2009; Jiang et al. 2008; Nakamura et al. 2007; Qu et al. 2009; Yoshikawa et al. 1998).

The majority of ginsenosides are steroids as they possess a four trans- ring rigid steroid skeleton (Attele et al. 1999; Wang et al. 2005) with sugar moieties attached (Cheng et al. 2005;
Nah. 1997). They share a triterpenoid saponin structure that is of the dammarane variety (Fuzzati. 2004) and are able to be differentiated from one another by the type of sugar moieties, sugar number, and site of sugar attachment at positions at carbon-3, carbon-6, or carbon-20 (Yuan et al. 2010). Isomerism, both structural and stereoisomerism, as well as the quantity and site of attachment of hydroxyl groups and available modified side chain at carbon-20 all act to further distinguish ginsenosides from each other (Yuan et al. 2010).

The ginsenosides from ginseng are separated into a variety of groups with protopanaxadiol (PPD) and protopanaxatriol (PPT) being the two major groups and ocotillol and oleanane groups are considered minor ones (Figure 1) (Qu et al. 2009; Wang et al. 2005). Moreover, dammarane saponins with a slightly altered steroid skeleton have been categorized as minor ginsenosides in Panax quinquefolius L. (Nakamura et al. 2007; Yoshikawa et al. 1998). Other isolated constituents are subdivided into nine different groups based on variations in the carbon-20 side chain (Jiang et al., 2008; Nakamura et al., 2007; Qiu et al., 2009). The PPD group has sugar moieties connected to the \( \beta \)-OH at carbon-3 and/or carbon-20, and the PPT group has sugar moieties attached to the \( \alpha \)-OH at carbon-6 and/or \( \beta \)-OH at carbon-20 (Jia and Zhao. 2009; Christensen. 2009; Wang and Yuan. 2008). The ocotillol group possesses a five-membered epoxy ring at C-20 and the oleanane group has a modified C-20 side chain (Yoshikawa et al. 1998).
Figure 1. Core chemical structure of four groups of ginsenosides from ginseng, i.e.,
protopanaxadiol (PPD) group, protopanaxatriol (PPT) group, ocatillol group, and oleanane
group. Ginsenoside Rf (in square) only exists in Asian ginseng, and pseudoginsenoside F11 (in
circle) is only found in American ginseng. Glc is an abbreviation for glycopyranoside (Mogil et
al. 1998) while rha refers to a rhamnose sugar (Lü et al. 2009) with the R standing for the side
chain. Figure from (Yuan et al. 2010).

From a chemical standpoint, there are several methods used to differentiate American
ginseng from Asian ginseng (Yuan et al. 2010). One difference is that in Asian ginseng, the
ginsenoside Rf is present, but in American ginseng it is absent (Shin et al. 2006). Conversely,
pseudoginsenoside F11 is present in American ginseng but not in the Asian variety (Shin et al.
2006). Another mechanism used to distinguish between these two types of ginseng is the ratio of
Rg1 to Rb1 as well as the ratio of Rb2 to Rb1 (Rg 1, Rb1, Rb2, and Rb1 are in all types of ginsenosides) (Yuan et al. 2010). When both ratios are under 0.4 it is typical of American ginseng while a greater value of these ratios is characteristic of Asian ginseng (Nakamura et al. 2007). Wild American ginseng is one exception because it can have a high Rg1 to Rb1 ratio (Schlag and McIntosh. 2006).

As for the bioavailability of ginsenosides, it has been suggested that the availability of intact ginsenosides as well as their metabolites in the intestines is very low (Karikura et al. 1990; Takino. 1994; Xu et al. 2003). For instance, a mere 3.29% of Rg1 and a minuscule 0.64% of Rb1 were identified in rat serum following ginsenoside ingestion (Han and Fang. 2006; Han et al. 2006). There was no measurable Rg1 in rat serum 24 hours following consumption while Rb1 concentration declined at a much slower rate and stayed fairly stable for 72 hours (Xu et al. 2003). It has been shown that the bioavailability of some ginsenosides can be enhanced by co-administrating them with adrenaline (Xiong et al. 2009) or by emulsifying those ginsenosides into a lipid based substance (Xiong et al. 2008; Han et al. 2009). Suppression of the p-glycoprotein efflux system has also been shown to increase the bioavailability of some ginsenosides (Xie et al. 2005). As for the half-life of ginsenosides, it has been said to be less than 24 hours in humans (Vuksan. 2007).

The quantity of ginsenosides in American ginseng, like the Asian variety, differs depending on the part of the plant (Yuan et al. 2010). The greatest ginsenoside content is found in the leaf (16.5 %), followed by root-hair (6.9%), rhizome (5.1%), root (4.9%) and stem (2.0%) (Qu et al. 2009). Further, in all parts of the plant other than the leaf, the quantity of ginsenosides increases with age (Zhang et al. 2008). Generally speaking, the key ginsenosides in American ginseng are Rb1, Re, Rd, Rc, Rg1, and Rb3 as they are responsible for more than 70% of the total
ginsenoside concentration in Panax quinquefolius L. (Qu et al. 2009; Wang et al. 2005; Lim et al. 2005). It has been suggested that Rb1, Re, and Rd are the major ginsenosides in American ginseng and Rb1, Rg1, and Rb2 are the major ginsenosides in Asian ginseng (Qi et al. 2011). Nevertheless, variability in individual ginsenosides as well as total ginsenoside concentration does exist and has been seen in various commercial products of American ginseng (Lim et al. 2005; Lin et al. 2010). Moreover, in addition to the age of the plant, there are other factors that impact the ginsenoside quantity including root dry weight (Wills et al. 2002), soil fertility (Li and Mazza. 1999), light exposure (Fournier et al. 2003), season (Kim et al. 1981; Li and Wardle. 2002) as well as geography/location (Li et al. 1996; Mudge et al. 2001; Yuan et al. 2001). This variability in ginsenoside content in various ginseng products could also be the reason for the different and sometimes contradictory physiological effects observed (Sengupta et al. 2004), which illustrates how crucial the standardization of ginseng products is (Yuan et al. 2010).

Through the use of heating or steaming, American red ginseng can be prepared in such a way so that it resembles Korean or Asian red ginseng (Wang et al. 2007). In fact, the chemical makeup of steamed American ginseng differs quite a bit from the non-steamed version (Yuan et al. 2010). As a result of the alteration in the ginsenoside makeup, the steaming treatment could boost some effects of American ginseng, such as enhancing its anti-cancer properties (Wang et al. 2007; Wang et al. 2006).

### 2.5 Ginseng and Muscle Damage

There are data to imply that it may be of assistance in recovery from exercise, specifically, in attenuating exercise-induced muscle damage, which is the basis for this thesis. Specifically, four weeks of American ginseng intake (1600 mg daily) in humans (cross-over
study) attenuated plasma creatine kinase, a marker commonly used to assess muscle damage, both during and following an exhaustive treadmill test at 80% VO$_2$max (Hsu et al. 2005). However, there was no improvement in a time to exhaustion treadmill test. It was hypothesized that the reduction in plasma creatine kinase was because of the ability of American ginseng to limit the amount of damage to the skeletal muscle cell membrane. While these data suggest that American ginseng may be an effective recovery aid following exercise, it did not utilize muscle strength measures. It has been suggested in the literature that reductions in muscle strength are one of the best indirect measures to denote muscle damage (Warren et al. 1999). In fact, several previous studies have pointed out that the emergence of muscle proteins in the blood is not a relevant marker of tissue damage (Van der Meulen et al. 1991; Kuipers. 1994; Komulainen et al. 1995).

Asian ginseng, specifically Korean red ginseng extract, has also been shown to attenuate exercise-induced muscle damage, markers of inflammation, as well as to enhance insulin sensitivity (Jung et al. 2011). In this study, 18 male college students consumed 20 g of ginseng three times per day or placebo for 11 days (seven days prior to a muscle damaging protocol, which was a high-intensity uphill treadmill run, and four days after). The ginseng group experienced significant reductions in plasma creatine kinase compared to the placebo group at 72 hours post-exercise. Additionally, at two and three hours following exercise, there were significant reductions in plasma interleukin-6 (IL-6), which is a marker often used to assess muscle inflammation with demanding exercise vs the placebo group (Armstrong et al. 1983; Minetto et al. 2005; Ostrowski et al. 1999; Pedersen et al. 1998). Furthermore, blood glucose and insulin responses in the ginseng group were both attenuated following a oral glucose tolerance test suggesting improvements in insulin sensitivity.
Although interesting, this study also did not utilize any muscle strength testing, which as mentioned, has been said to be amongst the best methods to assess muscle damage (Warren et al. 1999). Also, the huge 20 grams three times daily dose is not practical and may even bring about some undesirable side effects. Some of the adverse effects that have been associated with ginseng consumption include hypertension, difficulty sleeping, nausea, headache, nervousness, diarrhea, and fatigue (Miller. 1998; Vogler et al. 1999). Nevertheless, with more modest dosages it has been reported that “prolonged or excessive ginseng consumption involves very low risk to the user” (Chandler. 1988). Nevertheless, some degree of caution should still be exercised.

Although ginseng of either the Asian or American variety might attenuate muscle damage in humans, the precise mechanism by which it is able to do this has not been established and needs to be studied further (Jung et al. 2011). In an in vivo study conducted on Wistar rats, ginseng was shown to attenuate free radical production in skeletal muscle following exhaustive exercise (Voces et al. 2004), suggesting that anti-oxidant properties could explain how ginseng attenuates exercise induced muscle damage. Furthermore, in another rodent study, ginseng reduced lipid peroxidation through the inhibition of enzymes such as lipoxygenase (Cabral de Oliveira et al. 2001), which could explain its anti-inflammatory properties (Jung et al. 2011). A reduction in phospholipase A\textsubscript{2} activity could also be responsible for ginseng’s anti-inflammatory effects. (Liu and Chu. 1999).

Other rodent data shows that ginseng can reduce nitric oxide in muscle following an eccentric exercise protocol (Cabral de Oliveira et al. 2005). Interestingly, nitric oxide can decrease the force of contraction of the diaphragm and ventricular myocytes (Joe et al. 1998). Moreover, low nitric oxide could function as an anti-oxidant, protecting muscles from any harmful effects of exhaustive exercise (Reid. 1998; Perez et al. 2002). Additionally, ginseng
might offer protection against mitochondrial membrane damage as well as reduce protein oxidation (Cabral de Oliveira et al. 2005).

2.6 Factors Influencing Muscle Damage

Many exercise protocols can cause muscle damage. For example, lengthening (eccentric) contractions produce significant muscle damage vs shortening (concentric) contractions (Newham et al. 1983). Moreover, there are other factors that contribute to muscle damage, notably, the number of contractions, force, specific force and contraction velocity. As the number of lengthening contractions is augmented, a greater amount of muscle damage occurs (Talbot and Morgan. 1998). Further, faster eccentric contractions result in greater muscle damage than slower velocities (Lieber and Friden. 1993). Their study demonstrated that the amount of strain on the muscle fibres and, not necessarily high forces, determine the extent of muscle damage. They stretched two groups of rabbit tibialis anterior muscle to the same degree and at the same velocity but in one group (early stretch), the stretch coincided with onset of muscle activation, while in the other group (long stretch), muscle stretch was commenced 200 milliseconds after muscle activation. As a result, the muscles in the long stretch group generated a greater peak force than the early stretch group and despite the difference in force generation, the muscles in each group were damaged to a similar extent (Lieber and Friden. 1993). Furthermore, it has been shown that higher specific torque (higher frequency induced by electromyostimulation) resulted in more muscle damage than lower specific torque even when contraction velocity, range of motion, active muscle and contraction number were held constant (Black et al. 2008).
Muscle biopsies in humans have shown evidence of disrupted sacromeres following eccentric contractions, especially at the z disks (Newham et al. 1983; Raastad et al. 2010; Lauritzen et al. 2009), which results in damage to cytoskeletal proteins critical for the integrity of the sacromere (Friden and Lieber. 2001). With repetitive high intensity eccentric contractions, muscle damage is exacerbated as muscle fibre tension is increased resulting in damage to nearby z disks and sacromeres (Whitehead et al. 2003).

In addition to damage to the sacromeres, the mechanical stress to the muscle fibre may also cause damage to the excitation-contraction (EC) - coupling complex resulting in a reduction in force (Thiebaud. 2012). Specifically, it has been suggested that the EC- coupling complex is impaired precisely at the connection between the t-tubules and ryanodine receptors of the sarcoplasmic reticulum membrane, which are involved in mediating the release of calcium ions (Warren et al. 2001). In fact, data show that the junctophilin protein, which is a protein that enables a direct connection between the t-tubule and the ryanodine receptors, becomes impaired as a result of eccentric contractions and its damage is associated with a significant reduction in force (Corona et al. 2010).

Another mechanism involved in muscle damage is the activation of calcium proteases called calpains (Thiebaud. 2012). When ionic channels, such as stretch-activated calcium channels or transient receptor potential channels, are activated, there is an augmentation in intracellular calcium concentration (Allen et al. 2005). Further, elevated intracellular calcium occurs following the completion of eccentric contractions (Yeung et al. 2005). Increases in intracellular calcium activate calpains, which can subsequently cleave proteins such as titin, desmin, nebulin, troponin, tropomyosin, kinases, and other signaling molecules causing additional damage to the muscle (Allen et al. 2005). Nevertheless, the precise role of calpains in
muscle damage is not fully understood, as there are also data showing that large increases in calpain activity following eccentric movements does not correlate well with impairment to the myofibrils (Raastad et al. 2010). As the number of damaged muscle fibers begin to accrue, inflammation increases and there is an infiltration of the neutrophils and macrophages into the muscle fibre (Pizza et al. 2002), which ultimately help to activate satellite cells leading to muscle repair (Tidball and Villalta. 2010).

In summary, muscle damage seems to result from mechanical stress placed on the sacromeres during eccentric muscle contractions, which ultimately causes strain to various components of the muscle fibre including cytoskeleton, z-discs, plasma membrane, sarcoplasmic reticulum, as well as the myofibril itself. Furthermore, this mechanical stress can lead to activation of stretch-activated calcium channels or transient receptor potential channels, which cause intracellular calcium to rise, stimulating calpains and resulting in additional damage to muscle fibre proteins and eventually, an inflammatory response. In the end, muscle damage will lead to attenuation in force production, muscle soreness, an increase in blood proteins, such as creatine kinase and myoglobin, and edema of the exercised body part (Thiebaud et al. 2012).

2.7 Nutritional Supplements and the Attenuation of Exercise-Induced Muscle Damage

Previous data indicate that dietary carbohydrate and protein are helpful in attenuating the impairments in muscle function associated with exercise induced muscle damage (Cockburn et al. 2013) likely due to an enhancement of protein synthesis and attenuation of protein breakdown (Beelan et al. 2010) as well restoration of glycogen levels (Ivy. 1998). Furthermore, a variety of nutritional supplements including ginseng have been studied for their role in the prevention and
treatment of exercise-induced muscle damage. An extensive review article on this topic is available (Bloomer 2007). Relative to muscle damage induced by strength training, Bloomer concluded that the antioxidant vitamin C when taken alone as well as together with the antioxidant vitamin E may have the ability to reduce markers of muscle damage in untrained people. Further, flavonoids, when taken with mixed tocopherols and docosahexanoate, attenuate markers of inflammation in the untrained population, but did not have an effect on other markers of muscle damage. Also, there is a study reporting that branched chain amino acids (BCAA) (1 g isoleucine, 2.3 g leucine, 1.2 g valine) taken 15 minutes prior to exercise reduced delayed onset muscle soreness (DOMS) in women but not in men, perhaps due the lower relative dosage given to the men (Shimomura et al. 2006). Finally, there are data showing that HMB (β-hydroxy-β-methylbutyrate) taken at the same time as full body resistance training may be able to reduce creatine kinase and protein breakdown (as measured by urinary 3-methylhistididine) in untrained men, however, the fact that the subjects also ingested protein in addition to HMB may have confounded the results (Nissen et al. 1996).

In the strength-trained population, vitamin E can reduce creatine kinase (McBride et al. 1998) and L-carnitine can attenuate creatine kinase release, muscle soreness as well as tissue damage that was evaluated via an MRI (Volek et al. 2002). It was speculated that supplemental carnitine may possess antioxidant properties as well as the ability to help one maintain normal blood flow (Bloomer et al. 2007). Nevertheless, the evidence for all these nutrients is scarce due to the small number of participants studied (Bloomer. 2007).

Furthermore, in order for the nutritional supplements to have any effect, they may need to be ingested for days or weeks before the exercise, however, an ideal pretreatment time period has yet to be established nor is there much data comparing supplements consumed pre-exercise
versus post-exercise (or during exercise for that matter). Moreover, due to lack of data, the optimal dosage of these nutrients is unknown as is the effect that several of these nutrients used in conjunction would have on muscle damage (Bloomer. 2007).

Bloomer also mentioned that with the exception of L-carnitine, the effectiveness of many of these nutritional supplements is specific to non-resistance trained individuals (Bloomer. 2007). There are some data showing 1200 IU (international units) per day of vitamin E taken 2 weeks prior to exercise was able to attenuate creatine kinase release in strength-trained men (McBride et al. 1998). Also, two grams per day of L-carnitine taken for 3 weeks prior to exercise and four days in recovery reduced serum creatine kinase concentration, muscle soreness, and tissue damage, the latter being determined via an MRI, in strength-trained men (Volek et al. 2002). Moreover, a recent study showed that L-glutamine supplementation was able to attenuate post-exercise strength loss and muscle soreness in physically active men who performed drop jumps (Street et al. 2011). It should be noted that no supplement studied to date has been able to eliminate exercise-induced muscle damage, but some appear to attenuate its effects (Bloomer. 2007).

2.8 The Repeated Bout Effect

When unaccustomed exercise or exercise that is of a much greater volume, duration and/or intensity than done routinely is performed, the result is often muscle pain and weakness that is experienced for several days following the exercise (Nosaka and Aoki. 2011). Delayed onset muscle soreness (DOMS) and an extended loss of muscle function are common symptoms of muscle damage that is caused by eccentric contractions or isometric contractions at a long muscle length (Nosaka. 2008). However, when the same or a similar exercise is repeated within a
time frame of several weeks, even if no exercises are done in between, there is a significantly reduced or absence of pain felt post-exercise, which previously caused DOMS. This is known as the repeated bout effect (Nosaka. 2008; Nosaka. 2010).

One of the priorities of the present study is to cause DOMS through a downhill running protocol so it is critical to know how long subjects need to refrain from doing any downhill running or similar form of exercise. Currently, there is some debate as to how long the repeated bout effect lasts. Some suggest that it can last several weeks to several months (Miyama and Nosaka. 2004). Significantly reduced changes and faster recovery of indicators of muscle damage were observed for 2-4 weeks (Newham et al. 1987), 6 weeks-6 months (Nosaka et al. 1991), and 6 months (Nosaka et al. 2001). Nevertheless, it should be pointed out that all these studies involved high intensity eccentric exercise of the elbow flexors and not the knee extensors, which were the muscles that were damaged in the current study. For the lower extremity muscles, the repeated bout effect has been shown to last 4-13 days (Mair et al. 1995) and 3 weeks (Brown et al. 1997). Moreover, a downhill run study noted reduced muscle soreness and smaller increases in creatine kinase and myoglobin when a second bout of downhill running was repeated up to 6 weeks, but not 9 weeks following the first bout of downhill running (Byrnes et al. 1985). Also, a study involving drop jumps was shown to result in attenuated measures of muscle damage after the drop jumps were repeated 8 weeks following the initial bout of jumps (Miyama and Nosaka. 2004). It believed that there is a direct relationship between the amount of muscle damage incurred in the initial bout of exercise and the protective effect observed after the subsequent bout (Miyama and Nosaka. 2004). Due to the fact that drop jumps result in more muscle damage than downhill running, it was expected that the repeated bout effect would last longer than 6 weeks, which it did. For the present study involving bouts of
downhill running, we recruited participants who had not engaged in any extensive downhill endurance running in at least the previous 9 weeks.

One of the questions often associated with the repeated bout effect is exactly what are the mechanisms of this phenomenon? Although the precise mechanisms underlying the repeated bout effect have yet to be determined, a combination of mechanical, neural, and cellular adaptations are thought to play a role (McHugh et al. 1999; McHugh. 2003). The neural adaptations are said to consist of more efficient recruitment of motor neurons, increased synchrony of motor unit firing, better distribution of the workload among fibres, as well as an enhanced use of synergist muscles, and more slow-twitch fibre recruitment (Nosaka and Aoki. 2011). A repeated bout effect, consisting of attenuated muscle soreness and plasma creatine kinase concentration, was observed when comparing the first and second bout of electrically-stimulated isometric contractions of the knee extensors separated by two weeks (Aldayel et al. 2009). This provides some evidence that the repeated bout effect can still occur without or with limited contribution from the central nervous system. More evidence for neural factors playing a role comes from data which showed indications of a carryover effect (Howatson and van Someren. 2007). Howatson and van Someren reported that changes in muscle soreness, MVC strength, and serum creatine kinase activity were attenuated when a second bout of muscle damaging exercise was repeated on the contralateral arm 2 weeks later. Nevertheless, when comparing bout 1 and bout 2, the changes in muscle soreness and serum creatine kinase were greater in the ipsilateral group.

Others, however, feel that the underlying mechanisms of the repeated bout effect lie primarily within the muscle because one bout of muscle damaging exercise is not sufficient to cause alterations in neural drive (Kamandulis et al. 2010). Furthermore, there is a study
involving voluntary versus electrically stimulating eccentric exercise of the knee extensors, which showed an equal repeated bout effect between the two groups, indicating that changes in muscle recruitment are not responsible for the repeated bout (Black and McCully. 2008).

Several other ideas that have been suggested to explain the repeated bout effect, which include mechanical adaptations, such as, increases in passive or dynamic muscle stiffness, remodeling of intermediate filament system, increased intramuscular connective tissue, as well as cellular adaptations, including, longitudinal addition of sarcomeres, inflammatory response changes, alterations to maintain excitation-contraction coupling, strengthened plasma membrane, increased protein synthesis, increased stress proteins, and/or removal of stress-susceptible fibers (Nosaka. 2010). Moreover, it has been suggested that muscle fibres may even be lengthened less during a subsequent bout of eccentric exercise, hence, resulting in less damage (Nosaka and Aoki. 2011). Others have suggested that an upregulation of cytoskeletal protein and/or free radical scavenging pathways play a role in the repeated bout effect (Koh and Brooks. 2001). Further, the activation of the haemoxygenase-1 (HO-1) gene, caused by an augmentation in reactive oxygen and nitrogen species formation, may be related to the repeated bout effect (McArdle et al. 2004). Regardless, with all this debate it is quite clear that further research is needed in order to explain the mechanisms responsible for the repeated bout effect.

2.9 Tools to Measure Muscle Damage

They are a variety of methods that have been used to determine the extent of muscle damage including plasma creatine kinase concentration, muscle biopsies, magnetic resonance imaging (MRI), as well as assessments of muscle strength and function. Although creatine kinase has been widely used in the literature as a way to quantify muscle damage, there is some debate
in terms of its validity as a reflection of exercise-induced muscle damage (Baird et al. 2012). For example, some evidence suggests that creatine kinase by itself, may not offer a complete reflection of muscle damage (Mohaupt et al. 2009; Magal et al. 2010). Furthermore, there have been instances where reductions in creatine kinase did not result in similar decreases in delayed onset muscle soreness (McBride et al. 1998). Also, another study found that despite a similar degree of muscle soreness and ultrastructure z-band damage amongst various groups of comparable male subjects, creatine kinase concentration was inconsistent across the groups (Fielding et al. 2000). Further, hydration status prior to muscle damaging exercise can have an effect on plasma creatine kinase. Limitations to creatine kinase have also been explained through the “balloon analogy,” which is based on the idea that if the air within a blown up balloon represented creatine kinase concentrations (with the balloon representing the sarcolemma) and a hole was poked in the balloon (representing muscle damage), all of the air (creatine kinase) would be released through the balloon (sarcolemma) and into the outside area (which in this analogy would represent the bloodstream. In other words, even a small amount of damage to a muscle can result in an amount of creatine kinase being released into the bloodstream that may not be much different from that released when a slightly greater amount of muscle damage is incurred.

Meanwhile muscle biopsies are limited when it comes to using them to help assess muscle damage. Due to the fact that biopsies are specific to a very small area of examination, they may not reflect the extent of damage to the entire muscle (Baird et al. 2012). In other words, extrapolation cannot always be utilized when it comes to muscle biopsies and muscle damage. Moreover, the biopsy itself may result in damage to the muscle (Baird et al. 2012).
Muscle strength or function measures are another tool that has been used to assess the degree of damage to a muscle. It has been said that measures of muscle function, which were utilized in this study, may be the best way to determine the extent of exercise-induced muscle damage. Further in human studies, along with measurements of range of motion, measurements of maximal voluntary contraction torque may offer the best method to determine muscle injury (Warren et al. 1999). MRI is another method that can be used to evaluate muscle damage with elevated t2 relaxation times said to denote muscle damage (Leblanc et al. 2000). However, it involves considerable expense and consequently cannot be used routinely.

2.10 Summary, Purpose and Hypothesis

There is evidence in both humans and rodents to suggest that ginseng is capable of exerting a variety of positive pharmacological effects, much of which has been attributed to its ginsenosides. Going forward, there needs to be additional human data on ginseng supplementation to establish the proper dosage, for which populations that ginseng is most appropriate, as well as to document any its potential beneficial effects.

This thesis is focused on investigating whether ginseng can attenuate exercise-induced muscle damage. Some human data suggest that ginseng is capable of doing this, however, these studies did not utilize any measurements of muscle strength, which may be one of the best practical method in assessing muscle damage (Warren et al. 1999) because more direct assessments of muscle damage are limited, i.e., sampling problems (biopsies) or expense (MRI). Therefore, the purpose of this study was to assess the effects of American ginseng on muscle damage in humans using an outcome measure (muscle strength) that has not been used extensively in previous ginseng studies. The original plan was to use an aqueous ginseng extract
which in rodents reduced morphological signs of damage and inflammation compared to an alcohol extract (Estaki and Noble. 2012). However, this extract has not yet been approved for human use, so a Canadian grown American ginseng root powder (Rootalive Inc, Whitby, Ontario) was used in this study. Consequently, it was hypothesized that four weeks of American ginseng supplementation in humans would not reduce indices of muscle damage following an acute bout of downhill running relative to a placebo.
CHAPTER 3- METHODS
3.1 Participants

Ten men completed this study. An eleventh participant was unable to complete the study due to an injury to the calf and popliteal region of his leg, which was suffered in an activity separate from this research study. Exclusion criteria included extensive downhill endurance running in the previous 9 weeks, medication for depression or blood thinners (such as warfarin), and any known metabolic, musculoskeletal or neurological diseases (had women been included in the study we would have excluded those who were pregnant). This was verified using a previously approved health questionnaire (HSREB# 16912- see appendix 1) and having each participant complete the “Par Q and You Questionnaire” (Canadian Society for Exercise Physiology- see appendix 2). All were instructed to avoid any nutritional supplementation (including vitamins and/or minerals) during the study. Despite this instruction, upon follow-up one subject in the ginseng group revealed that he consumed omega 3 supplements during the study. His data were still included in the study as they did not appear to be consistently different from the other subjects when looking at individual data pertaining to percent change from baseline measures and observing each of the time points amongst the three variations in muscle contraction. Further, it could be hypothesized that if omega 3’s were going to reduce muscle damage it would be through anti-inflammatory mechanisms. A recent review article stated that human data are inconclusive as to whether omega 3 polyunsaturated fatty acids are able to able to limit the inflammatory and immunomodulatory response to exercise when taken at the suggested dosage of approximately 1-2 g/d of EPA and DHA at a 2:1 EPA: DHA ratio.

Participants were able to continue their normal exercise routine, but were told not to add any new physical activity. The majority of participants were recreationally active, meaning that while they engaged in exercise (no endurance/downhill running), none were serious athletes.
training to maximize their athletic potential nor were any a member of a varsity team. All possible risks or discomforts were explained fully prior to any testing and all participants provided written, informed consent. The study was conducted in the Exercise Research Nutrition Laboratory (ERNL) and the Wolf Orthopaedics Biomechanics Laboratory (WOBL). Prior to any testing, the study was approved by the Office of Research Ethics at Western University.

### 3.2 Experimental Overview

This double-blind study commenced with participants reporting to the ERNL where they were debriefed regarding the nature of the study. Participants proceeded to the WOBL for a familiarization day with the Biodex® (Biodex Medical Systems Incorporated, Shirley, NY) strength test device. Each replicated the protocol he would perform later during baseline and post-downhill run isometric and isokinetic leg extensor strength by going through the protocol once as a warm-up and then a second time giving a full effort. This familiarization day was conducted at least two days prior to performing baseline testing. The first four subjects in this study (two in each group) did not have a familiarization day and only performed submaximal contractions just prior to executing the baseline testing. This was modified subsequently because it was felt that in order to minimize any learning effect from influencing the data performing maximal effort testing prior to baseline testing was best. Nevertheless, the data from the last six subjects were similar to the first four subjects so all baseline strength data were included.

After the participants completed their baseline measures of leg extensor strength, they were given a supply of either American ginseng (450 mg capsules) or a placebo (500 mg inulin fibre) and instructed to take four capsules throughout the day (1.8 g/d) with food/meals for four the next weeks. Neither the researcher nor the participants knew who was given ginseng or
placebo in order to maintain the double blind nature of the study. This was done by having an individual not involved in the study label capsule containers with a code. The 1.8 g/d came out to 24.5 mg/kg/d on average for the ginseng group. As for how this relative dosage compares to some other ginseng studies that involve animals, a rat study illustrated anti-oxidant effects of Panax ginseng extract when given at 10mg/kg or 100mg/kg daily for 3 months (Voces et al. 2004) and an additional study concluded that Panax ginseng was able to protect muscle from injury induced by eccentric exercise in rats when given at a daily dosage of 100mg/kg daily for 3 months (Cabral de Oliveira et al. 2005). Meanwhile, the relative daily dosage in the American ginseng study in humans by Hsu et al. 2005 was, worked out to about 22.8 mg/kg daily, which was similar to the relative dosage used in this study.

After four weeks of supplementation, participants reported back to the ERNL where they performed a downhill run on a treadmill broken up into five, eight minute running bouts (9.7-11.3 km/h at -12% grade). One of the subjects was unable to complete the downhill running protocol having to stop midway through his third of the five, eight minute running bouts. His data were included in the study as his muscle strength results illustrated that he completed enough of the protocol to cause muscle damage.

At one, two and three days after the downhill run, participants repeated the Biodex® measures of leg extensor strength exactly as they had performed it four weeks earlier. Supplementation was continued during the post-run measures. Also, during each of these measurement times, participants rated their level of muscle soreness on a scale of one to ten with one representing virtually no soreness and ten representing the highest degree of pain or soreness (Maimer et al. 2012). Baseline soreness was assumed to be 1 as the participants had not done any recent eccentric exercise. Other studies that have involved subjects providing some sort of self
determination of muscle soreness have shown that subjects tend to provide quite low values of soreness at baseline (Leahy and Pintauro. 2013; Hilbert et al. 2003). Participants also completed an incremental treadmill test and had their oxygen consumption (\( \dot{V}O_2 \text{max} \)) as well as a body composition (lean mass and fat mass) via air displacement (Bod Pod®) densitometry (for details, see below). Further, a three day food record was completed by the participants, at a time which was convenient for them, whether that was prior to, during, or post ginseng or placebo consumption. The purpose of these were simply for descriptive data on the subjects.

### 3.3 Strength Measures

**Isometric Peak Torque**

Isometric peak torque of the dominant leg extensors was assessed using the Biodex® device in accordance with the manufacturer’s instructions both prior to and following supplementation. Briefly, isometric torque was assessed at a joint angle of 80 degrees because this knee angle has been demonstrated to elicit maximal torque values for isometric knee extensor exercise (Byrne et al. 2001). Participants performed three maximal voluntary contractions (MVC) of the quadriceps for five seconds with one min of rest between each one. The average peak torque of the three measures was recorded. Just prior to the MVC, participants performed a period of warm-up where they performed the same testing protocol, but using submaximal contractions at a self-selected effort level.

**Isokinetic Concentric Peak Torque**

Measurements of isokinetic concentric peak torque of the knee extensors were conducted at angular velocities of 60 and 180 degrees/sec using the same Biodex® device as described
above. These testing speeds were based off a recent study published in the *Journal of Strength and Conditioning Research* by Nunan et al. 2010. Moreover, according to the Biodex® website, slow speeds (60-120 degrees/second) are considered “strength speeds” and fast speeds (180-300 degrees) are known as “endurance speeds” (Biodex® Medical System Inc.). Hence, the two different testing speeds allowed us to assess muscle performance using two speeds that are categorically different.

The isokinetic contractions were performed immediately following the isometric measures and the protocol entailed three maximal efforts conducted at each angular velocity and the average value was recorded. Participants performed three MVC consecutively at 60 degrees/sec, followed by one minute of rest and then performed the three consecutive MVC at 180 degrees/sec.

### 3.4 Downhill Running Protocol

After four weeks of ginseng supplementation, the participants each performed an intermittent downhill running protocol on a treadmill, designed to elicit muscle damage (Eston et al. 2000; Nunan et al. 2010). Briefly, the downhill running protocol consisted of a total of 40 min of running divided into five, eight min bouts at between 9.7 and 11.3 kilometres per hour (6 and 7 miles per hour) and -12% grade. Between the bouts of running subjects were permitted two minutes of active recovery (walking). Prior to the downhill run, participants were allowed to perform a five min self-paced warm-up at 0% grade. One participant chose not to perform the warm-up prior to the run. Subjects were permitted to have water ad libitum.

The -12% grade was verified as the inverse tangent ratio to determine the required angle of inclination. The inverse tangent of 12 divided by 100 is 6.8 degrees; hence, the back of the
treadmill was propped up and secured at this angle using pieces of wood (verified with an inclinometer).

### 3.5 Body Composition

Body composition (lean mass and fat mass) was determined in the ERNL via whole body densitometry using air displacement plethysmography for volume and an accurate weigh scale for mass (Bod Pod®, Life Measurements, Concord, CA). Testing procedures were in accordance with the manufacturer’s instructions as detailed in the manual. Briefly, the participants wore tight shorts (either compression shorts or boxer brief underwear) and a tightly fitted bathing cap on their head, thoracic gas volume was estimated for all participants through the use of a predictive equation essential to the Bod Pod® software, and all refrained from eating or exercising for at least two hours prior to the test. Each participant’s height (cm) was determined prior to the body composition measurement using a double ruler body scale (Health o meter ®). All calculations were completed by system software. Body composition (as well as maximal oxygen uptake) measurements were done on the subjects only for descriptive data.

### 3.6 Maximal Oxygen Uptake

Maximal oxygen uptake (\(\dot{V}O_2\text{max}\)) was determined in the ERNL with a Vmax® metabolic cart (V6200, Sensormedics Corporation, Yorba Linda, CA) using breath-by-breath measurements during an incremental graded running test on a Woodway® treadmill (Woodway USA Inc., Waukesha, WI). Participants began the test at a comfortable running speed (9.7-11.3 kilometres per hour) with a 0% incline. Each minute, the incline was increased 2% until volitional fatigue. Prior to the test, participants were instructed to go as long as they could and
taught how to safely get off the treadmill when they had reached volitional fatigue. Data were averaged over 30 sec and the greatest value was taken as the $\dot{V}O_2$max. Heart rate was monitored during the test using a Polar Wearlink®+ transmitter.

### 3.7 Food Record

All participants in the study compiled a food diary in which they recorded everything they ate for three consecutive days. Four of the participants completed a food record on their own as it coincided with an academic assignment they were doing during the semester which required them to conduct a dietary analysis diet. The rest of the participants used a Taylor® (Taylor Precision Products, Las Cruces, NM) Classic Digital Kitchen Scale to use to weigh their food. From there, the food records were analyzed using the online program “eaTracker,” which was produced by Dietitians of Canada to calculate energy intake and macronutrient values. One subject did not complete a food record, but he did confirm that he did not alter his diet during his participation in the study.

### 3.8 Ginseng and Placebo Capsules

The American Ginseng Vegi-Capsules consumed in the study were provided by Rootalive Inc., which is based in Whitby, Ontario. According to Rootalive, the capsules were formed from premium grade Canadian grown American Ginseng root and each capsule contained 450 mg. of 100% pure American ginseng, i.e., no fillers, yeast, binders, flow agents or preservatives were added to the capsules. They were not subject to any type of aqueous or alcohol extraction method and had a ginsenoside content of 5.53%. The American ginseng used in the study by Hsu and colleagues in 2005 had a ginsenoside composition of the following;
8.67% for Rb1, 0.99% for Rc, 1.05% for Rd, and 5.08% w/w (percent concentration weight/total weight of solution) for Re (Hsu et al. 2005).

The placebo capsules used in this study were assembled in the ENRL using a Cap-M-Quik® (S.L. Sanderson and Company, Berry Creek, CA) Size “1” Capsule Filler and size 1 gelatin capsules (Empty Capsules Company, Murrieta, CA), capable of holding ~300 to 600 mg depending on the density of the powder. The capsules were filled with Life Brand® inulin fibre, which contained five calories and three grams of fibre per 3.2g teaspoon. Consequently, neither the energy nor the fibre would be expected to affect the placebo participants due to the minute quantities consumed.

3.9 Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics. The strength measures were evaluated using a mixed factor 2 x 4 (treatment x time) repeated measures ANOVA. The ratings of perceived muscle soreness were evaluated using a mixed factor 2 x 3 (treatment x time) repeated measures ANOVA. Treatment by time interaction effects as well as main effects for group and time were assessed. Mauchly’s sphericity test was used to check the homogeneity of variance and when the assumption of sphericity was violated, it was corrected using the Greenhouse-Geisser adjustment. A significance level of p<0.05 was set prior to analyses and if a significant difference was identified, pairwise comparisons with a Bonferroni correction were used to locate the difference. Furthermore, all values were reported as mean ± standard deviation values rounded to the nearest tenth, and the graphs were constructed using Microsoft Excel.
CHAPTER 4 - RESULTS
4.1 Participant Data

The men were approximately 21 years old and were similar in terms of height, body mass, VO$_2$max, body fat as well as age (Table 1). There were no significant differences between the groups in any of the characteristics using one-way ANOVA and an alpha of p=0.05.

Table 1. Physical characteristics of participants (means ± SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n=5</th>
<th>Ginseng n=5</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>20.4 ± 2.3</td>
<td>21.4 ± 1.5</td>
<td>0.441</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.0± 6.2</td>
<td>174.8 ± 4.9</td>
<td>0.826</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>67.9 ± 13.7</td>
<td>73.4 ± 7.13</td>
<td>0.446</td>
</tr>
<tr>
<td>$\dot{V}$O$_2$max ml.kg$^{-1}$.min$^{-1}$</td>
<td>58.2± 6.4</td>
<td>54.7 ± 7.9</td>
<td>0.458</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>11.1 ± 1.5</td>
<td>15.4 ± 5.6</td>
<td>0.136</td>
</tr>
</tbody>
</table>

*Value significantly different from placebo (p<0.05)

4.2 Self Rating of Muscle Soreness

There was a significant main effect for time (p < 0.01) on participants’ rating of their muscle soreness (muscle soreness on day 3 was significantly lower than both days 1 and 2, but there was no significant difference between days 1 and 2 post-run). There was no main effect for group (p=0.222) nor was there a group by time interaction effect (p=0.279) (Fig 2). One participant was unable complete the downhill running protocol but still complained of soreness in the days following it (ratings of 10, 9, and 7 on days 1, 2, and 3 respectively) so his data were included. Although baseline self ratings of muscle soreness were not actually taken, going by the aforementioned assumption that they would be quite low based on prior studies, it is reasonable
to expect that soreness values on each post-run day would be significantly greater than at baseline, particularly post-run days 1 and 2.

Figure 2. Perceived rating of muscle soreness one, two, and three days following the downhill run. A 1-10 rating scale was used with 1 representing the lowest or no soreness and 10 representing the highest degree of soreness. Participants were able to select half values (i.e. 6.5). Values are mean ± SD for placebo (n=5) and ginseng (n=5) groups. There were no significant differences between groups.

*Value significantly different from placebo (p<0.05).
4.3 Isometric Contractions

There was no main effect for group (p=0.478) nor was there a main effect for time. Although the p value for the effect of time was 0.021, once a Bonferroni correction was used on the pairwise comparisons it was determined that were no significant difference between any of the time points. Furthermore, there was no group by time interaction effect present (p=0.182).

The overall pattern of response was similar between placebo and ginseng groups, which saw a decrease in force on post day 1, followed by a recovery on post days 2 and 3; however this trend was more evident in the ginseng compared to the placebo group, which was more consistent throughout (figure 3). In the placebo group, torque, in comparison to baseline values, decreased by 8.9± 15.4%, 2.3 ± 9.8, and 0.1 ± 15.1% on one, two, and three days after the downhill run respectively. In the ginseng group, torque decreased by 12.3 ± 15.6% compared to baseline one day following the downhill run, but then on days two and three following the run, it increased 4.2 ± 12.2% and 8.4 ± 8.2%, respectively. All percentage data was calculated by analyzing each subject in each group’s individual percent change from baseline and tabulating the group means and standard deviations from those values.
*Value significantly different from placebo (p<0.05).

Figure 3. Absolute peak torque values for isometric contractions of knee extensors. Torque was assessed at a knee angle of 80 degrees. Values are means ± SD for placebo (n=5) and ginseng (n=5). There were no significant differences between the groups. All torque values were measured in newton metres (N-M).

**4.4 Isokinetic Contractions at 60 Degrees/Second**

The main effect of group was not significant (p=0.556) and neither was the main effect of time (p=0.219). There was also no group by time interaction either (p=0.542). Like the isometric
contractions, the overall blueprint for the ginseng group was similar and consisted of a decrease in force on post day 1 followed by a recovery on the next day and then maintenance on the third post run day. The data points in the placebo group exhibited less variability throughout. In comparison to baseline values, torque in the placebo group decreased 2.2 ± 11.9% one day after the downhill run then subsequently increased 2±14.9% and 3.4± 18.4% on days two and three after the downhill run, respectively. Meanwhile, in the ginseng group, torque decreased each day after the run when compared to baseline with reductions of 12.5 ±13.5%, 5.8 ± 11%, and 7.4 ± 6.5% on days one, two, and three respectively. There was no significant difference between the baseline measures of the two groups (Fig 4).

*Value significantly different from placebo (p<0.05).*
Figure 4. Absolute peak torque values for isokinetic contractions of knee extensors performed at a speed of 60 degrees per second. Values are means ± SD for placebo (n=5) and ginseng (n=5). There were no significant differences between the groups. All absolute torque values were measured in N-M.

4.5 Isokinetic Contractions at 180 Degrees/Second

Once again, there was no main effect for group (p=0.735) nor time (p=0.179). There also was no group by time interaction effect present either (p= 0.893). The overall pattern of response mimics the ones seen in the other types of contractions in that in both groups there was a reduction in force on post day 1 followed by recovery and maintenance on the subsequent days. Data points were slightly less variable in the placebo group. On the first day after the downhill run, the placebo group had a reduction in torque of 6.1 ± 11.7% compared to baseline then a subsequent increase of 0.7 ± 13.4% and 2.2 ±12.8% on days two and three, respectively. The ginseng group had a reduction of torque, relative to baseline, on all three days following the downhill run of 10.1 ± 10.4%, 3.1 ± 7.3%, and 1.7 ± 14.5% on days one, two and three days after, respectively. Once again, there was no significant difference in the baseline measures between the two groups (Fig 5).
Figure 5. Absolute peak torque values for isokinetic contractions of knee extensors performed at a speed of 180 degrees per second. Values are means ± SD for placebo (n=5) and ginseng (n=5). All torque values were measured in N-M.

*Value significantly different from placebo (p<0.05).
CHAPTER 5- DISCUSSION
5.1 Overview and Major Findings

The purpose of this study was to investigate whether American ginseng supplementation in young men attenuates indices of muscle damage following a downhill running protocol, which was designed to initiate muscle damage. In order to accomplish this, muscle strength measures of the knee extensors as well as self-ratings of muscle soreness were studied in a double blind study (ginseng supplemented group vs a placebo group). The participants in the ginseng and placebo subjects were similar in terms of age, height, mass as well as in cardiovascular fitness (\( \dot{V}O_2 \text{max} \)) and body composition (body fat percentage).

The downhill running protocol was effective in causing the subjects to experience a sensation of muscle soreness as evidenced by the ratings of perceived muscle soreness. This was expected because it is well established that exercise where eccentric contractions predominate, such as downhill running, causes muscle damage especially in those unaccustomed to that type of exercise (Clarkson and Newham. 1995). Further, the numerical rating scale (NRS) used to assess soreness is “valid, reliable, and appropriate for use in clinical practice” (Williamson and Hoggart. 2005) and this type of rating scale has good sensitivity, produces data that are able to undergo a statistical analysis, and is highly reproducible (Brunelli et al. 2010). While these comments are in reference to the 11 point, 0-10 NRS, the 1-10 numeric rating scale that was employed in this study is essentially identical and has been used previously to assess subjective pain (Maimer et al. 2012). Based on this rationale, the observed lack of significant difference between the ginseng and placebo groups in the measured self-ratings of muscle soreness suggests that the exercise protocol used induced a similar degree of muscle damage in both groups.

Although there were no significant effects of time for peak torque at any point during the study, this may have been complicated by the large variability between subjects. For instance, for
the isometric contractions, at day 1 post-run, there was an 8.9 and 12.3% decrease in peak torque from baseline in the placebo and ginseng groups, respectively. In a study by Nunan et al. 2010, a comparable 9% decrease in peak torque in both a treatment and placebo group one day following a similar downhill running protocol was significant. Moreover, in the present study isokinetic contractions (60 degrees per second) on day 1 post-run reductions in peak torque of 2.2 and 12.5% were observed in the placebo and treatment group, respectively compared to 7.5 and 5.8% in Nunan’s study. For the isokinetic contractions (180 degrees/second), reductions in torque of 6.1 and 10.1% were observed in the placebo and treatment group respectively compared to 7.4 and 5.8% in Nunan’s study. All of these reductions were significant in Nunan’s study, while the present reductions were not likely due to the observed variability. Consequently, it appears the present study was under powered.

The gluteus muscles, quadriceps, and calf muscles were amongst the areas where subjects complained of soreness from the downhill running protocol. Moreover, there is a trend for subjects to experience deterioration in torque on the first day after the downhill run, albeit, non-significantly (Figures 3-5).

5.2 Limitations

One of the limitations of this study was the large variability in the muscle strength measures amongst the subjects as well as a small n. Consequently, finding a between group effect was difficult. The data also suggest that there was also no effect of time on torque values of the knee extensors, but again, finding a difference was made difficult due to the large variability and limited participants. Furthermore, it is possible that a learning effect occurred in some of the subjects confounding the muscle damaging effects of the downhill run. Although a
familiarization protocol was in place, it may not have provided subjects with sufficient time to become accustomed to the machine. However, a similar study investigating the effects of beta-hydroxy-beta-methylbutyrate and alpha-ketoisocaproic acid supplementation on exercise-induced muscle damage used a warm-up protocol consisting of two sub-maximal contractions and one maximal contraction and did not mention a learning effect (Nunan et al. 2010). Also, there are data that have observed no learning effect with the Biodex® machine and mentioned it to be very reliable (Lund et al. 2005). Nevertheless, it is something to at least consider, especially when someone is naïve to performing a certain skill or protocol.

Another possible limitation worth bringing up is the fact that there was some within group variability in the activity level of the subjects, which may explain at least some of the variation in decrements in average peak torque. Although the subjects in the study were unaccustomed to extensive downhill running, some subjects were less active than others and thus, may have been more susceptible than others to exercise-induced muscle damage. Another thing pertaining to the subjects worth mentioning are the food records, which in this study were only done to gain descriptive data on the subjects. In general, it has been shown that people have a tendency to underestimate their energy consumption (de Vries et al. 1994).

An additional aspect of this study that turned out to be a limitation was the number of pills that the participants were instructed to ingest. The large number of daily pills (four) over an extended period of time resulted in some subjects forgetting to take a pill at some point during the course of the study. For the most part, the participants did follow directions and take the pills, however, several subjects had pills leftover at the conclusion of the study including one subject in the ginseng that had 31 pills that he did not consume. This means his dose was actually 1350 mg/d not 1800mg as designed. However, only his isokinetic contraction data at 60
degrees/second appeared to differ compared to the others. Specifically, he experienced a much more severe reduction in force (32, 25, and 16% on days one, two, and three following the downhill run, respectively compared to the group average of 12, 6, and 7%). However, this subject was also the most unfit in the study and he was unable to complete the entire downhill running protocol, which may have contributed to the force drop off. Ironically, this subject had a larger recovery in force for the isokinetic contractions at 180 degrees/second on day 3 post downhill run (about 19% greater than baseline compared to the group average of -2%). Consequently, it is unlikely that this inconsistency resulted from the lower dosage.

There were also three other subjects in the ginseng group that did not consume all their pills, (three, six, and 10 pills, respectively but any effect here would be minimal as missing 10 pills over the study is only 4.5 g of a dose totaling 54 g). The placebo group had two subjects with pills leftover at the study conclusion (five and 11, respectively) and one subject who ran out prematurely.

Another factor which likely played a role in the results is the type of ginseng used in this study. One of the limitations that is present when studying ginseng is the difficulty in establishing a standardized version that can be used across various studies. The concentration of ginsenosides, the major active component in ginseng, as well as amount of individual ginsenosides in the plant can be altered by cultivation conditions, such as, soil, temperature, moisture, length of cultivation, and harvest season. Hence, ginseng could have differing effects depending on the location where it is cultivated (Yuan et al. 2002). For instance, in a pharmacological study in rodents, extracts of American ginseng cultivated in the United States had greater inhibitory effects than American ginseng that was grown in China (Yuan et al. 1998). Additionally, American ginseng grown in the same country, but different locations has also been
shown to cause a variation in ginsenoside concentration. For example, aqueous extracts of
American ginseng grown in the state of Illinois contained approximately 30% less of the
ginsenoside Rb1 and 25% more ginsenoside Re than did American ginseng that was produced in
the state of Wisconsin (Yuan et al. 2001).

Additional challenges relate to the fact there can be variability in herbal products not only
from manufacturer to manufacturer, but also from lot to lot (Winslow and Kroll. 1998).
Furthermore, there have been discrepancies found between the ginsenoside concentration on
ginseng labels and the ginseng concentration actually measured (Harkey et al. 2001).

5.3 Is Exercise Induced Muscle Damage Beneficial or Detrimental?

Finally, another important consideration is even if ginseng is able to limit exercise-
induced muscle damage is this beneficial? Although exercise-induced muscle damage causes
muscle soreness and a reduction in force production, it has been debated whether this damage
and soreness is a necessary stimulus to cause beneficial adaptations such as muscle hypertrophy.
In other words, if we were to attenuate muscle damage and alleviate muscle soreness post-
exercise, would we limit any adaptations to the prior workout? Some recent data suggest that
post-exercise cold baths or cold water immersion, a common recovery modality used by athletes
and fitness enthusiasts may help in recovery in the short-term but may hamper long term strength
training adaptations, although the effects were said to be small (Fröhlich. 2014). Furthermore,
there are data suggesting that muscle damage is needed to stimulate muscle hypertrophy. For
instance, eccentric strength training is well-known to induce more muscle damage than
concentric strength training and there is evidence that eccentric training may lead to greater gains
in strength and muscle mass versus concentric strength training (Roig et al. 2009).
In contrast, while these studies suggest that eccentric exercise is superior to concentric exercise in terms of leading to muscle hypertrophy, it is critical to consider the total amount of work being performed (Thiebaud et al. 2012). Specifically, an intriguing study completed at McMaster University in Hamilton, Ontario (Moore et al. 2012) where muscle hypertrophy gains between eccentric and concentric strength training were compared when both total work and training intensity were matched is of interest. The eccentrically-contracted limb (elbow flexor) performed significantly more work than the concentrically-contracted limb per repetition (68 kJ/rep vs 42 kJ/rep), so the concentrically-trained limb executed 40% more contractions in order to match the total work of the eccentrically contracted limb. After 9 weeks, the investigators concluded that when it comes to eccentric vs concentric resistance training, similar gains in muscle hypertrophy and strength can be achieved when training intensity and work output are matched. In other words, it is the exercise stimulus itself and not the nature of the contraction that produces gains in muscle strength and hypertrophy (Moore et al. 2012).

Moreover, another study where muscle damage was induced in one group but not the other by using a recumbent ergometer with pedals that pushed toward the subject, thus allowing for eccentric contractions to occur is relevant. In this study, one group (pre-trained) underwent 11 weeks of eccentric lower body strengthening, including 3 weeks of pre-training where intensity and duration were gradually increased, followed by 8 weeks where intensity and duration were maintained. The other group (naïve) was introduced to the training protocol in week four (meaning they only performed 8 weeks of eccentric lower body strengthening) and did not gradually increase their intensity and duration. Consequently in the first week, the naïve group experienced significant increases in plasma creatine kinase as well as a significantly greater degree of perceived muscle soreness, as measured using a visual analog scale. The total
cumulative workload completed by the two groups was matched even though the length of the protocols between the two groups was different (11 vs 8 weeks). Importantly, after several weeks of training, no differences in muscle hypertrophy and strength were found between the two groups, evidence that one can obtain strength gains and muscle hypertrophy in the absence of significant muscle damage and soreness (Flann et al. 2011).

Finally, a recent review paper concluded that muscle damage does not seem to be necessary to promote muscle hypertrophy, but that more studies examining microtears and molecular events that are not revealed through indirect markers such as creatine kinase, force and soreness are needed (Thiebaud. 2012). So, muscle damage may not be necessary in order to help muscle recover from a subsequent bout of similar exercise. In other words, the repeated bout effect (performing the same or similar exercise within a certain time frame results in less damage than the initial bout [McHugh et al. 1999; Nosaka et al. 2001; Nosaka. 2008; Nosaka. 2010]), may occur even if muscle damage does not occur in the initial exercise bout (Thiebaud. 2012), but it may be augmented with increasing amounts of muscle damage (Miyama and Nosaka. 2004).

5.4 Future Direction

Future studies should include greater subject numbers as well as ensuring adequate familiarization of the strength testing equipment has occurred to eliminate any learning effects. Furthermore, future studies could benefit from having something that alerts subjects to take their daily pills as this may reduce the likelihood of subjects forgetting (perhaps an automated text alert). It would also be interesting to see prospective studies evaluate the validity of some of the health claims stated by ginseng marketers, such as, reduction in stress and fatigue, increase in
physical stamina, and reduction in severity of the common cold. As well, it would be ideal if future ginseng studies attempted to use a standardized version allowing better comparison across studies, however, as detailed earlier, this can be difficult.

Of course, as it pertains to ginseng and muscle damage, future research should include the use of an aqueous ginseng extract with a higher ginsenoside yield, assuming that it meets safety guidelines, as well as larger sample sizes, and a combination of strength and blood plasma measures. Also an effort to standardize the diet of the participants as well as blood measures to assess how much of the ginsenosides or other ginseng components were absorbed into the bloodstream could also be implemented in future research.

Moreover, well downhill running has been shown to cause damage in the quadriceps, it has also been shown to cause damage to the gluteus muscles as well as the anterior and posterior tibial (shin and calf muscles respectively) muscles (Eston et al. 1994). Perhaps investigation on the extent of muscle damage in these other areas could be something worth examining in the future. A localized test for muscle soreness could also be something that could be utilized in the future to quantify the extent of muscle damage. For instance, a spring-loaded pressure device on areas of damaged tissue could be used and participants could subsequently rate their level of muscle soreness on a numeric rating scale.

The repetition of the baseline measures on different days could also be done in the future in order to evaluate the degree of biological variability amongst the subjects in the study in terms of the muscle strength measures. Magnetic resonance imaging (MRI) measures would also be helpful as they would provide an objective quantification of the damaged muscles so that the location and extent of the damage could be analyzed more completely.
5.5 Summary

Ginseng has been said to have been utilized in some form for over 2000 years with the commonly held belief that it enhances life expectancy due to its ability to cure a wide variety of ailments (Yuan et al. 2002). For this study, it was hypothesized that four weeks of American ginseng supplementation, which had not undergone any extraction methods and consisted of only ground ginseng root, would be unable to reduce indices of muscle damage in young males following an acute bout of muscle damaging exercise, which in this case, was downhill running. The inability of this form of ginseng to attenuate signs of muscle damage was reflected by similar peak torque values of the knee extensor muscles during muscle strength measures consisting of isometric and isokinetic contractions between a ginseng consuming group and a placebo group.

Ten young men completed this study and each of them underwent initial baseline testing consisting of muscle strength measures while consuming either American ginseng or placebo (inulin fibre) capsules for four weeks in addition to their normal daily diet. Following these four weeks, all participants performed a downhill running protocol designed to cause muscle damage and were then asked to repeat the initial muscle strength measures at one, two, and three days following the downhill run. The peak torque values for each of the three types of muscle contractions (isometric, isokinetic at 60 degrees/sec, isokinetic at 180 degrees/sec) were each analyzed separately and there were no significant differences found between the two groups, which coincided with the initial hypothesis. This suggests that ground American ginseng root is of little value when it comes to reducing muscle damage following a bout of eccentric exercise.

In general, a proper diet as well as post exercise consumption of carbohydrates and protein has also shown to be an asset to one’s recovery from exercise (Cockburn et al. 2013).
While some dietary supplements may reduce exercise induced muscle damage, this may not be the ideal option as not only does it appear that they need to be consumed for several days or weeks prior to the exercise in order to work (Bloomer. 2007), thus bringing about the potential risk of toxicity, but some supplements, such as vitamin C and E may actually hamper some beneficial adaptations to exercise such as improved insulin sensitivity by inhibiting the activation of ROS (reactive oxygen species) induced molecular regulators of insulin sensitivity, namely PGC 1α, PGC 1β, and PPARγ. (Ristow et al. 2009). Vitamin C and E supplementation may also blunt endurance training induced rise in mitochondrial proteins, although vo2 max was unaffected. The exact mechanism for these results has yet to be specified (Paulsen. 2014). High intakes of antioxidants through supplementation may inhibit the body’s natural ability to adapt to oxidative stress (Peternelj and Coombes. 2011). Some data even suggest that dietary antioxidant supplements may raise markers of inflammation as opposed to reducing them (Peternelj and Coombs. 2011). Hence, one should be cautious when choosing to consume nutritional supplements for whatever reason as more is certainly not always necessary and may even be detrimental.

In the end, the best way to curb muscle damage or soreness following a bout of exercise is to perform an exercise that one is familiar with or has performed within the last several weeks in order to ensure that the repeated bout effect will occur. It is also essential that unaccustomed activities be introduced gradually if limiting post-exercise muscle soreness is a priority. As for ginseng, future studies focusing on larger sample sizes as well as the use of an aqueous extract would allow for further insight into its ability to attenuate exercise induced muscle damage.
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Appendix A

Participant Information

Subject I.D.: ____________ Date: _________________

Age: ________________ Height: ________________ Weight: ________________

Smoker: Yes / No Ethnic Background: ____________________

Medical History (please check any and all that apply)

Family history of heart disease □
Heart murmur □
Phlebitis □
Other heart disorder (please specify) □
Family history of stroke □
Migraines □
Sinus problems □
Hypertension □
Diabetes □
Raynaud’s syndrome □
Polycystic ovary syndrome □
Seizures □
Digestive problems □
Asthma □
Bronchitis □
Other respiratory disorder (please specify) □

Have you ever fainted? Yes / No

If yes, under what circumstances: __________________________________________________
______________________________________________________________________________
______________________________________________________________________________

Are you taking any medications? Yes / No

If yes, please specify: _______________________________________________________________________

Have you consumed alcohol or any caffeinated beverages in the last 12 hours? Yes / No

If yes, please specify the quantity: _______________________________________________________________________

Have you had any major surgeries, illnesses or injuries? Yes / No
If yes, please specify (include dates): _______________________________________________

Are you physically active?   **Yes / No**

If yes, please specify the type, frequency, and typical duration of exercise:
______________________________________________________________________________

How long have you been physically active?
______________________________________________________________________________

Age of menarche:  ________________
Appendix B

Appendix C

GINSENG AND EXERCISE

The Effect of American Ginseng on Exercise-Induced Muscle Soreness

We are currently looking for healthy 18-35 year old men and women to participate in a research study investigating the effects of American ginseng intake on exercise-induced muscle soreness.

Measures: Muscle strength, muscle soreness ratings, and Magnetic Resonance Images before and after an exercise bout

You can participate if you are:

- 18-35 years old
- Healthy
- Able to jog for 8 minutes
- Have not engaged in any endurance run training in the previous 9 months

You can NOT participate if you:

- Are injured
- Are diabetic
- Have an upcoming surgery
- Are pregnant or breast-feeding
- Have insomnia or difficulty sleeping
- Any history of head or eye injury involving metal fragments
- Have some type of implanted electrical device (i.e. cardiac pacemaker)
- Have severe heart disease including susceptibility to heart rhythm abnormalities
- Have conductive implants or devices such as skin patches, body piercing or tattoos containing metallic inks

If you have questions about this study or would like to participate please contact Brent Smith
## Appendix D

### Food Records- Energy and Macronutrient 3-Day Average Intakes (Rounded to Nearest Whole Number)

<table>
<thead>
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<th>Subject #</th>
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<th>Carbohydrate (g)</th>
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Appendix E

Certificate of Approval of Human Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Peter Lemon
File Number: 102333
Review Level: Full Board
Approved Local Adult Participants: 32
Approved Local Minor Participants: 0
Protocol Title: The effect of American ginseng on exercise-induced muscle soreness
Department & Institution: Health Sciences/Kinesiology, Western University
Sponsor: 
Ethics Approval Date:
Ethics Expiry Date: December 31, 2013

Documents Reviewed & Approved & Documents Received for Information:

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<td>Western University Protocol</td>
<td>(including instruments noted in section 8.1)</td>
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<td>Letter of Information &amp; Consent</td>
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This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/CH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRR registration number IRR 00000040.

Ethics Officer to Contact for Further Information

<table>
<thead>
<tr>
<th>Name</th>
<th>Email Address</th>
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<tr>
<td>Janice Sutherland</td>
<td><a href="mailto:jsuther@uwo.ca">jsuther@uwo.ca</a></td>
</tr>
<tr>
<td>Grace Kelly</td>
<td><a href="mailto:grace.kelly@uwo.ca">grace.kelly@uwo.ca</a></td>
</tr>
<tr>
<td>Shantel Wallott</td>
<td><a href="mailto:swallott@uwo.ca">swallott@uwo.ca</a></td>
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</table>

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6A 3K7 t: 519.661.3036 f: 519.660.2460 www.uwo.ca/research/services/ethics
Appendix F

Letter of Information

Title of Study: The effect of American ginseng on exercise-induced muscle soreness

You are being invited to participate in a research study conducted by P.W.R. Lemon (PhD), Brent Smith (BA), Kole Abbott (BSc), Alan Smith (BSc), Terry Olver (MSc), Kristine Beaulieu (BSc), Adam Upshaw (MSc) and Arash Bandegan (MSc), from the Exercise Nutrition Research Laboratory in the School of Kinesiology at Western University.

If you have any questions or concerns about the research, please feel free to contact Brent, Kole, Alan, Kristine, Terry, Adam, Arash or Dr. Lemon

PURPOSE OF THE STUDY

The purpose of this research is to determine if four weeks of American ginseng intake at 1800 mg. per day will attenuate muscle soreness and/or injury following exercise.

INCLUSION/EXCLUSION CRITERIA

In order to be eligible to participate in this study you must be a healthy, 18 to 35 year old male or female who has not performed any endurance run training in the past 9 months.

You will be excluded from this study if you report that you are: injured, diabetic, pregnant (or any chance you may become pregnant), breast-feeding, an insomniac, schizophrenic or if you are a female with endometriosis or uterine fibroids. Furthermore, you will also be excluded if you are taking warfarin, medication for diabetes or depression, have high or low blood pressure, or have surgery scheduled within two weeks following the completion of this study.

PROCEDURES

If you volunteer to participate in this study, we will ask you to do the following things:
1. Complete a simple health survey (PAR-Q) to assess your current physical capability.
2. Consume 1800 mg of American ginseng daily for four weeks leading up to a downhill jog test as well as throughout the time for post-run measures (a few days).
3. Complete a downhill jog on a treadmill (similar to jogging down a small hill). This downhill test will consist of five, eight minutes bouts of jogging with two minutes of recovery (walking) in between each bout.
4. Complete three, three second maximal static muscle contractions of the leg extensors (muscles that straighten the knee) and three maximal voluntary contractions at each of two different angular speeds (60 degrees/second and 180 degrees/second) using a strength testing machine (Biodex) before and 24, 48, and 72 hours after the downhill jog test.
5. A select few individuals will be asked to undergo an MRI (Magnetic Resonance Imaging) evaluation before and three days after the downhill run. This involves lying on a bed in a confined space for about 20 minutes. If you are selected for the MRI there additional exclusion criteria (see MRI section below).

Testing will be conducted in the Exercise Nutrition Research Laboratory, Wolf Orthopaedic Biomechanics Laboratory, and St Joseph’s Health Care Centre at Western University.

TIME INVOLVED

This study will take place over the course of approximately four and a half weeks. There will be a four week supplementation period, which will be followed by a 40 minute downhill jogging test (consisting of five, eight minute bouts with two minutes of walking recovery in between each bout) and four muscle strength testing sessions, three of which will take place at 24, 48, and 72 hours following the downhill run and the other will take place prior to beginning supplementation.

Following the baseline measures of muscle strength on the Biodex, you will come to the Exercise Research Nutrition Research Lab for approximately to obtain your ginseng and to receive instructions about when to take it over the following 4.5 weeks (with meals). The muscle strength tests, which will take a total of approximately 40 minutes to complete (10 minutes on each of 4 test time points). Those that are selected to undergo the MRI will have two additional 20 minute assessment times (one prior to and one following the downhill run test).
POTENTIAL RISKS AND DISCOMFORTS

All exercise involves some health risk (primarily heart/blood vessels or fluid-related) but lack of physical activity has been shown to more hazardous to one’s health. Further, these concerns are much reduced in young, healthy individuals. Similar exercise to the type being used in this study is completed daily by Western students in kinesiology classes, in intramural sports, and by Mustang athletes. Participants can expect to feel some muscle soreness from this experiment (similar to any unaccustomed exercise) which will resolve in a matter of days. You will be encouraged to drink additional fluids to replace any perspiration losses.

American ginseng is generally considered safe and is widely available as an over the counter product in many grocery or health food stores throughout Canada. Many come with a GMP (good manufacturing practices) certification, which considers standard operating procedures, employee training, product specifications, expiration dating, vendor certifications and much more. In terms of popularity, according to well-known botanist Dr. James Duke, America exports close to $100 million of American ginseng each year and about 6 million Americans use some form of ginseng regularly. However, there are some people who are best to avoid American ginseng (those people will be excluded for this study). Specifically, American ginseng use has been associated with insomnia, irritability, nervousness, or restlessness, but these effects are usually mild and transient. Further, there is some chance that this form of ginseng could cause low blood sugar when taken in large amounts. This is avoided if taken with meals which will be done in this study. The Biodex strength machine has been used widely here and around the world and there are no risks associated with it other than those associated with any exercise.

MRI

Some of you in this study will be asked to undergo an MRI (Magnetic Resonance Imaging) before and after the downhill running protocol. MRI is a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field, and a radio frequency field. No X-rays are used. As with any technology there is a risk of death or injury. For MRI the risk of death is less than 1 in 10 million and the risk of injury is less than 1 in 100 000. These risks do not arise from the MRI process itself, but from a failure to disclose or detect MRI incompatible objects in or around the body of the subject or the scanner room. It is therefore very important that you answer all the questions honestly and fully on the MRI screening questionnaire. Almost all deaths and injuries related to MRI scans have occurred because the MRI operator did not know that surgically implanted metal hardware (such as a cardiac pacemaker) was present inside the
subject during the MRI scan. Other remote risks involve temporary hearing loss from the loud noise inside the magnet. This can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the scan. For comparison, the risk of death in an MRI is similar to travelling 10 miles by car, while the risk of injury during an MRI is much less than the risks associated with normal daily activities for one hour. Some examples that will prevent you from receiving an MRI include having some MRI incompatible metal in your body, being pregnant or attempting to become pregnant, or having a drug patch on your skin that contains metal foil. Should you require a medically necessary MRI scan in the future, the final decision as to whether you can be scanned will be made by a qualified physician considering all risks and benefits.

MRI exclusion criteria

If you have any history of head or eye injury involving metal fragments, if you have some type of implanted electrical device (such as cardiac pacemaker), if you have severe heart disease (including susceptibility to heart rhythm abnormalities), you should not have an MRI scan unless supervised by a physician. Additionally, you should not have a MRI scan if you have conductive implants or devices such as skin patches, body piercing or tattoos containing metallic inks because there is a risk of heating or induction of electrical currents within the metal element causing burns to adjacent tissue.

POTENTIAL BENEFITS

The results of this study will help to determine the effectiveness of American ginseng in humans on attenuating muscle soreness following downhill running.

COMPENSATION
You will not be compensated for your participation in this study.

CONFIDENTIALITY
Any information that is obtained in connection with this study that can identify you will remain confidential and will be disclosed only with your permission. This information will be collected on a master list that will be kept in a password protected file with access to only the investigators in this study. All data will be collapsed before results are printed (only group averages and variability). All participants will be assigned an arbitrary number to ensure
anonymity. Mean data will be stored in a password protected file for comparison with future studies. Raw data will not be released to any other parties.

PARTICIPATION AND WITHDRAWAL
You can choose whether to be in this study or not. If you are a student and you volunteer, you may withdraw at any time without any effect on your status at Western. If you are not a Western student, you may withdraw from the study at any time. You may also refuse to answer any questions you feel are inappropriate and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE SUBJECTS
We plan to publish this study in a reputable academic journal upon the completion of the research. The information published in a journal or subsequent studies will not identify you in any way. Copies of such articles will be available upon request.

SUBSEQUENT USE OF DATA
These data may be used in subsequent studies but the data will have no personal identifiers. You will receive a copy of the consent form after it has been signed. You do not waive any legal rights by signing the consent form.

This letter is for you to keep. If you have any questions about this research project, feel free to call us (Dr. Peter Lemon / Brent Smith, Kole Abbott, Alan Smith, Kristine Beaulieu, Terry Olver, Adam Upshaw, or Arash Bandegan) for clarification. Further, if you have any questions about the conduct of this study or your rights as a research subject you may contact the Office of Research Ethics at Western University.

Sincerely,
Dr. Peter Lemon / Brent Smith / Kole Abbott / Alan Smith / Kristine Beaulieu/ Terry Olver / Adam Upshaw / Arash Bandegan

Principal Investigators

RM 2235 3M Centre UWO, Exercise Nutrition Research Laboratory
Appendix G
Letter of Informed Consent

The effect of American ginseng supplementation on exercise-induced muscle soreness

Investigator:  P.W.R. Lemon (Brent Smith)

I have read the accompanying "Letter of Information", have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

By signing below, I agree to participate in this study.

Name of Participant (please print):
_______________________________________

Signature of Participant: ____________________________      Date: __________________
_______________________________________

Name of Person Obtaining Informed Consent:
_______________________________________
Signature of Person Obtaining Informed Consent:


Date: ______________________

RE-RECRUITMENT IN FUTURE STUDIES

If you wish to participate in future studies in the Exercise Nutrition Research Lab, please include your current contact information below.

I wish to be contacted for future studies in the Exercise Nutrition Research Laboratory.

Yes_____ (check mark), No _____ (check mark)

If yes, email __________________  Date: ______________________
CURRICULUM VITAE

Name: Brent E. Smith

Education:

The University of Western Ontario
London, Ontario
Kinesiology, B.A.
2006-2010

The University of Western Ontario
London, Ontario
Kinesiology, M. Sc.
2010-2014

Related Work Experience:

The University of Western Ontario
Graduate Teaching Assistant
2010-2011