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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 Master of Science degree in Kinesiology

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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

Western University

London, Ontario, Canada

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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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# 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, anti-oxidation, 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, anti-oxidation, 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, "Jijuzhang (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 wangianus 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 β-OH at carbon-3 and/or carbon-20, and the PPT group has sugar moieties attached to the α-OH at carbon-6 and/or β-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).

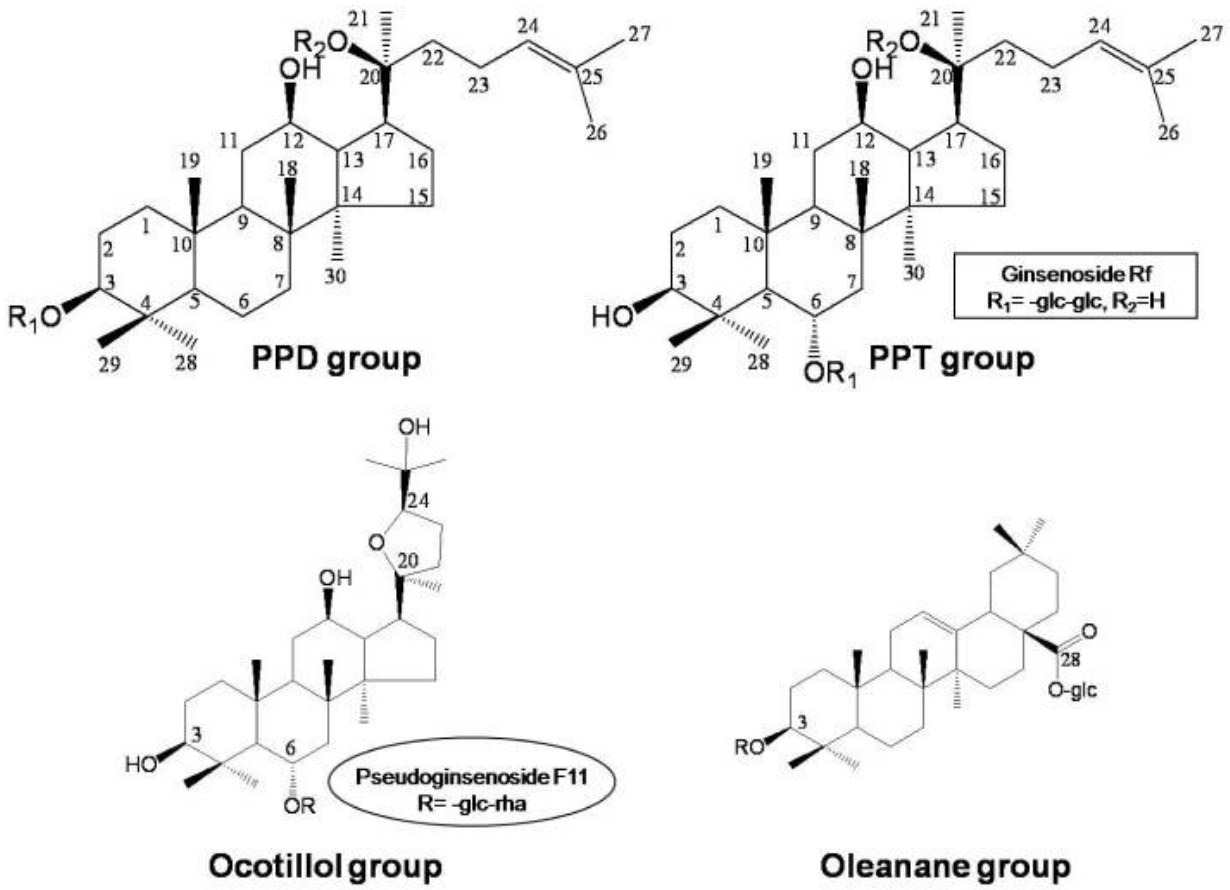



Figure 1. Core chemical structure of four groups of ginsenosides from ginseng, i.e., protopanaxadiol (PPD) group, protopanaxatriol (PPT) group, ocotillol group, and oleanane group. Ginsenoside Rf (in square) only exists in Asian ginseng, and pseudoginsenoside F11 (in circle) is only found in American 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 $Rb_1$, 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 $A_2$ activity could also be responsible for ginseng's anti-inflammaotry 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-hydroy-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-methylhistidine) 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 haemoxygenease-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 ( $\dot{V}O_2max$) 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 ( $\dot{V}O_2max$) 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 $\dot{V}O_2max$. 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, pairwaise 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, $VO_2max$, 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)

| Characteristic | Placebo n=5 | Ginseng n=5 | P- value |
|---|---|---|---|
| Age (y) | 20.4 ± 2.3 | 21.4 ± 1.5 | 0.441 |
| Height (cm) | 174.0± 6.2 | 174.8 ± 4.9 | 0.826 |
| Body mass (kg) | 67.9 ± 13.7 | 73.4 ± 7.13 | 0.446 |
| $\dot{V}O_2max$ $ml.kg^{-1}.min^{-1}$ | 58.2± 6.4 | 54.7 ± 7.9 | 0.458 |
| Body Fat (%) | 11.1 ± 1.5 | 15.4 ± 5.6 | 0.136 |

*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

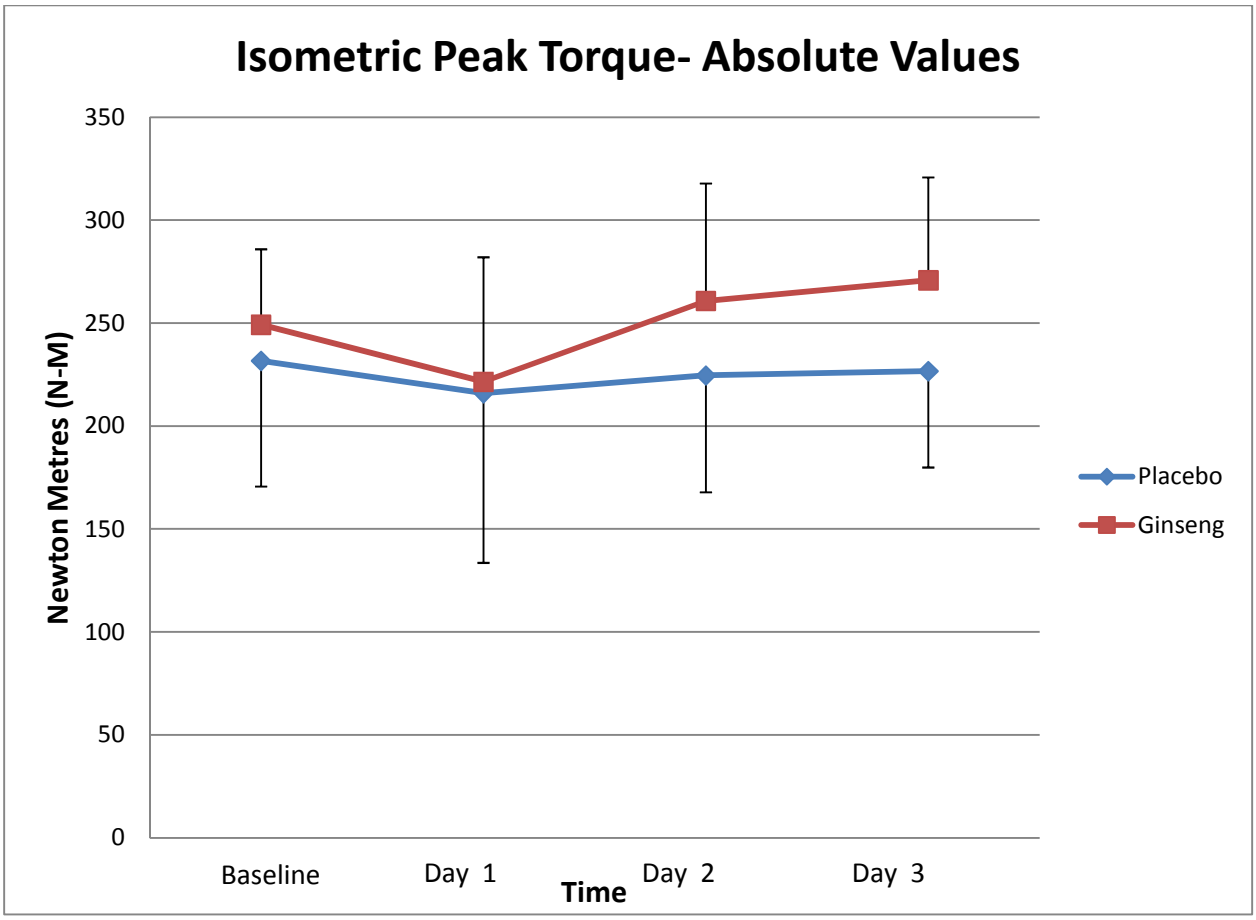
to expect that soreness values on each post-run day would be significantly greater than at baseline, particularly post-run days 1 and 2.

*Value significantly different from placebo ($p<0.05$).

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.

## 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.



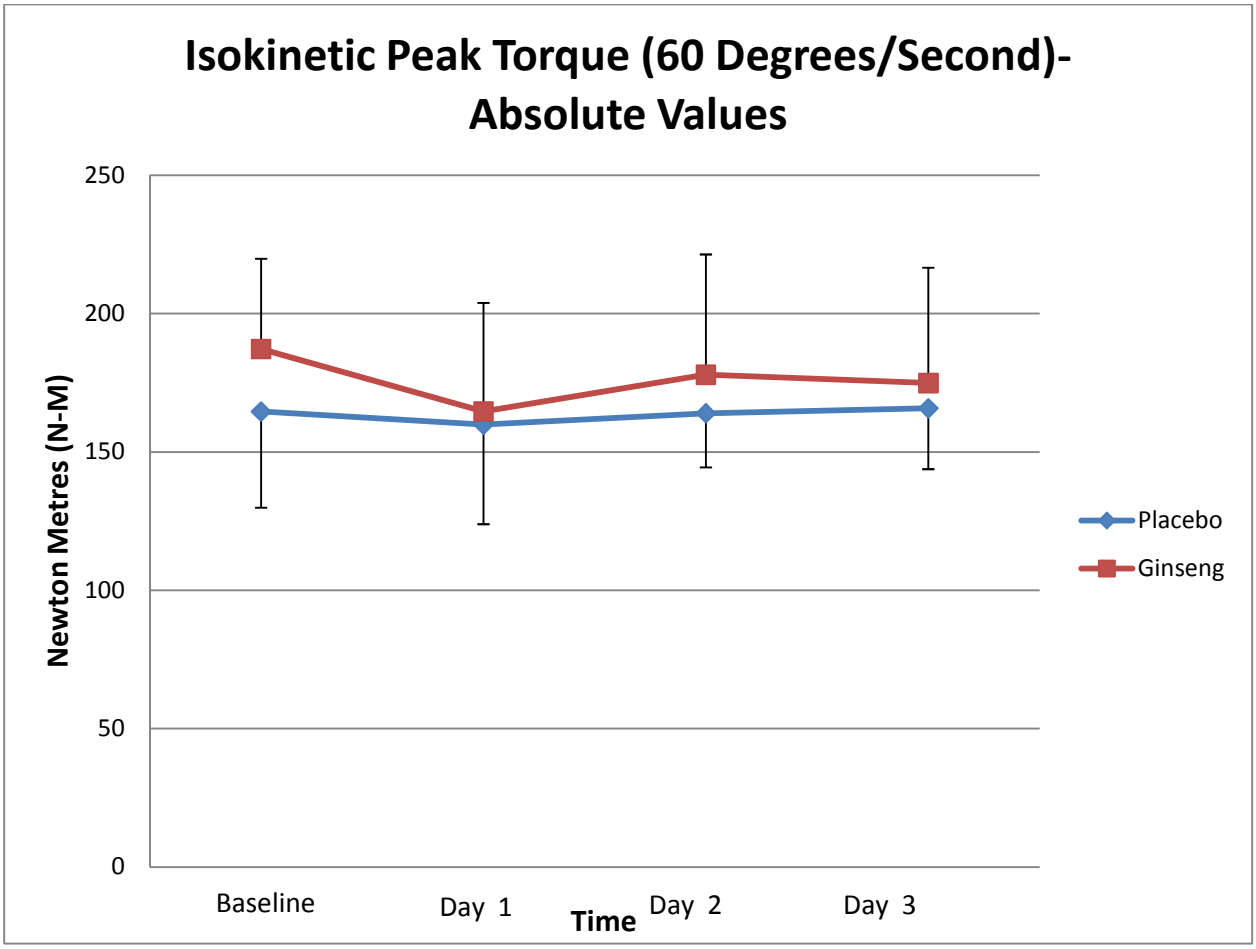

*Value significantly different from placebo ($p<0.05$).

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).

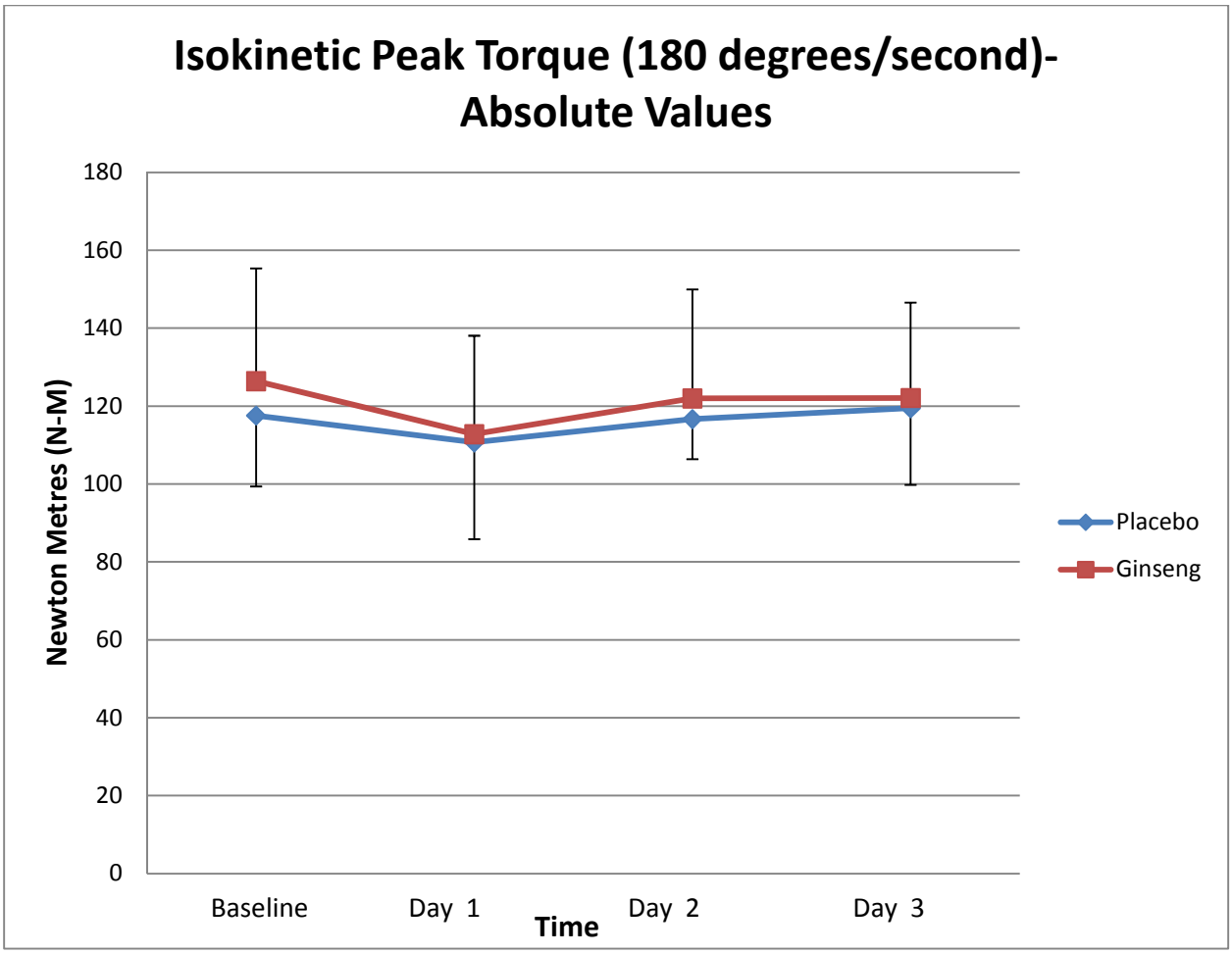



*Value significantly different from placebo ($p<0.05$).

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).




*Value significantly different from placebo ($p<0.05$).

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.

# 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 ( $\dot{V}O_2$ 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 ginsenosdies 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.

References

Abad CC, Ito LT, Barroso R, Ugrinowitsch C, Tricoli V. (2010). Effect of classical massage on subjective perceived soreness, edema, range of motion and maximal strength after delayed onset muscle soreness. *Brazilian Journal of Sports Science, 16*(1), 36-40.

Achike FI, Kwan CY. (2003). Nitric oxide, human diseases and the herbal products that affect the nitric oxide signaling pathway. *Clinical and Experimental Pharmacology and Physiology, 30*(9), 605-615.

Aggarwal BB, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B. (2009). Molecular Targets of Nutraceuticals Derived from Dietary Spices: Potential Role in Suppression of Inflammation and Tumorigenesis. *Experimental Biology and Medicine (Maywood, NJ), 234*(8), 825–849.

Agriculture and Agri-Food Canada, Canada's North America Ginseng. Retrieved from http://www5.agr.gc.ca/resources/prod/Internet-Internet/MISB-DGSIM/CB-MC/PDF/5270-eng.pdf

Aiken J, Bua E, Cao Z, Lopez M, Wanagat J, McKenzie D, McKiernan S. (2002). Mitochondrial DNA deletion mutations and sarcopenia. *Annals of the New York Academy of Sciences, 959,* 412-423.

Aldayel A, Jubeau M, Mcguigan MR, Nosaka K. (2010). Less indication of muscle damage in the second than initial electrical muscle stimulation bout consisting of isometric contractions of the knee extensors. *European Journal of Applied Physiology, 108*(4), 709-717.

Allen DG, Whitehead NP, Yeung EW. (2005). Mechanisms of stretch-induced muscle damage in normal and dystrophic muscle: role of ionic changes. *Journal of Physiology, 567*(Pt 3), 723-735.

Ang-Lee MK, Moss J, Yuan CS. (2001).Herbal medicines and perioperative care. *The Journal of the American Medical Association, 286*(2), 208–216.
Armstrong RB. (1984). Mechanisms of exercise-induced delayed onset muscular soreness: a brief review. *Medicine and Science in Sports and Exercise, 16*(6), 529-538.

Armstrong RB, Ogilvie RW, Schwane JA. (1983). Eccentric exercise-induced injury to rat skeletal. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology, 54*(1), 80-93.

Asano K, Takahashi T, Miyashita M, Matsuzaka A, Muramatsu S, Kuboyama M, Kugo H, Imai J. (1986). Effect of Eleutheroccocus senticosus extract on human physical working capacity. *Planta Medica, (3), 175-177.*

Assinewe VA, Baum BR, Gagnon D, Arnason JT. (2003). Phytochemistry of wild populations of Panax quinquefolius L. (North American ginseng). *Journal of Agricultural and Food Chemistry, 51*(16), 4549–4553.

Attele AS, Wu JA, Yuan CS. (1999). Ginseng pharmacology: multiple constituents and multiple actions. *Biochemical Pharmacology*, *58*(11), 1685–1693.

Attele AS, Wu JA, Yuan CS. (1999). Ginseng pharmacology: multiple constituents and multiple actions. *Biochemical Pharmacology, 58*(11), 1685–1693.

Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, Yuan CS. Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component. *Diabetes, 51*(6), 1851–1858.

Aung HH, Mehendale SR, Wang CZ, Xie JT, McEntee E, Yuan CS. (2007). Cisplatin's tumoricidal effect on human breast carcinoma MCF-7 cells was not attenuated by American ginseng. *Cancer Chemotherapy and Pharmacology, 59*(3), 369–374.

Azike CG, Charpentier PA, Hou J, Pei H, King Lui EM. (2011). The yin and yang action of North American ginseng root in modulating the immune function of macrophages. *Chinese Medicine, 6*(1), doi: 10.1186/1749-8546-6-21.

Bahrke MS, Morgan WP. Evaluation of the ergogenic properties of ginseng: an update. *Sports Medicine (Auckland, N.Z.), 29*(2), 113-133.

Baird MF, Graham SM, Baker JS, Bickerstaff GF. (2012). Creatine kinase and exercise related muscle damage implications for muscle performance and recovery. *Journal of Nutrition and Metabolism, 2012*, Article ID 960363.

Bao HY, Zhang J, Yeo SJ, Myung CS, Kim HM, Kim JM, Park JH, Cho J, Kang JS. (2005). Memory enhancing and neuroprotective effects of selected ginsenosides. *Archives of Pharmacal Research, 28*(3), 335–342.

Baranov A. (1966). Recent advances in our knowledge of the morphology, cultivation and uses of ginseng (Panax ginseng C.A. Meyer). *Economic Botany, 20*(4), 403-406.

Baranov AI. (1982). Medicinal uses of ginseng and related plants in the Soviet Union: recent trends in the Soviet literature. *Journal of Ethnopharmacology,* 6(3), 339-353.

Barnes AS, Powell-Griner E, McFann K, Nahin RL. (2004). Complementary and alternative medicine use among adults. *Advance Data*, 27(343), 1–19.

Beelen M, Burke LM, Gibala MJ, van Loon L JC. (2010). Nutritional strategies to promote postexercise recovery. *International Journal of Sport Nutrition and Exercise Metabolism, 20*(6), 515-532.

Benishin CG, Lee R, Wang LC, Liu HJ. (1991). Effects of ginsenoside Rb1 on central cholinergic metabolism. *Pharmacology, 42*(4), 223–229.

Bensky D, Gamble A, Kaptchuk T, Eds. (1993). *Chinese herbal medicine: Materia medica* (pp. 314-317). Vista, CA: Eastland Press.

Bittles AH, Fulder SJ, Grant EC, Nicholls MR. (1979). The effect of ginseng on lifespan and stress responses in mice. *Gerontology*, *25*(3), 125-131.

Black C, Elder CP, Dudley GA. (2008). High specific torque is related to lengthening contraction induced skeletal muscle injury. *Journal of Applied Physiology, 104*(3), *639-647.*

Black CD, McCully KK. (2008). Muscle injury after repeated bouts of voluntary and electrically stimulated exercise. *Medicine and Science in Sports and Exercise, 40*(9), 1605-1615.

Bloomer RJ. (2007). The role of nutritional supplements in the prevention and treatment of resistance exercise-induced skeletal muscle injury. *Sports Medicine, 37*(6), 519-532.

Blumenthal M. (2002). Herb sales down in mainstream market, up in natural food stores. *Herbalgram*, (55), 60.

Borchers AT, Keen CL, Stern JS, Gershwin ME. (2000). Inflammation and Native American medicine: The role of botanicals. *The American Journal of Clinical Nutrition, 72*(2), 339–347.

Brekhman II, Dardymov IV. (1969). New substances of plant origin which increase nonspecific resistance. *Annual Review of Pharmacology, 9,* 419-430.

Brekhman II. (1965). Eleutherococcus senticosus: a new medicinal herb of the araliaceae family. In: Chen KK, Mukerji B (Eds.), *Pharmacology of Oriental Plants* (pp. 97-102). New York (NY): Macmillan Company.

Brown SJ, Child RB, Day SH, Donnelly AE. (1997). Exercise induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *Journal of Sports Sciences, 15*(2), 215-222.

Brunelli C, Zecca E, Martini C, Campa T, Fagnoni E, Bagnasco M, Lanata L, Caraceni A. (2010). Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. *Health and Quality of Life Outcomes, 8,* 42.

Buettner C, Yeh GY, Phillips RS, Mittleman MA, Kaptchuk TJ. (2006). Systematic review of the effects of ginseng on cardiovascular risk factors. *The Annals of Pharmacotherapy,* 40(1), 83–95.

Byrne C, Eston RG, Edwards RH. (2001). Characteristics of isometric and dynamic strength loss following eccentric exercise-induced muscle damage. *Scandinavian Journal of Medicine and Science in Sports, 11*(3), *134-140.*

Byrnes WC, Clarkson PM, White JS, Hsieh SS, Frykman PN, Maughan RJ. (1985). Delayed onset muscle soreness following repeated bouts of downhill running. *Journal of Applied Physiology, 59*(3), 710-715.

Cabral de Oliveira AC, Perez AC, Merino G, Prieto JG & Alvarez AI (2001). Protective effects of *Panax ginseng* on muscle injury and inflammation after eccentric exercise. *Comparative Biochemistry and Physiology. Toxicology and Pharmacology: CBP*, *130*(3), 369-377.

Cabral de Oliveira AC, Perez AC, Prieto JG, Duarte IDG, Alvarez AI. (2005). Protection of Panax ginseng in injured muscles after eccentric exercise. *Journal of Ethnopharmacology, 97*(2), 211-214.

Cartwright L. (1979). Ginseng in pharmacies. *Australian Journal Pharma*cy,60, 346-349.

Chandler RF. (1988). Ginseng and health. *Canadian Pharmacists Journal,158*, 36-38.

Chen CF, Chiou WF, Zhang JT. (2008). Comparison of the pharmacological effects of Panax ginseng and Panax quinquefolium. *Acta Pharmacologica Sinica*, *29*(9), 1103–1108.

Chen LM, Zhou XM, Cao YL, Hu WX. (2008). Neuroprotection of ginsenoside Re in cerebral ischemia-reperfusion injury in rats. *Journal of Asian Natural Products Research,* 10(5-6), 439–445.

Chen XC, Huang TW, Zhang J, Song JQ, Chen LM, Zhu YG. (2008). Involvement of calpain and p25 of CDK5 pathway in ginsenoside Rb1's attenuation of beta-amyloid peptide(25–35)-induced tau hyperphosphorylation in cortical neurons. *Brain Research, 1200,* 99–106.

Cheng Y, Shen LH, Zhang JT. (2005). Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. *Acta Pharmacologica Sinica, 26*(2), 143–149.

Cheng Y, Shen LH, Zhang JT. Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. (2005). *Acta Pharmacologica Sinica, 26*(2), 143–149.

Cheng Y, Shen LH, Zhang JT.(2005). Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. *Acta Pharmacologica Sinica, 26*(2), 143-149.

Cheung K, Hume PA, Maxwell L. (2003). Delayed onset muscle soreness: treatment strategies and performance factors. *Sports Medicine, 33*(2), 145-164.

Chong SKF, Oberholzer VG. (1988). Ginseng: is there a use in clinical medicine? *Postgraduate Medical Journal, 64*(757), 841-846.

Christensen LP. (2009). Ginsenosides chemistry, biosynthesis, analysis, and potential health effects. *Advances in Food and Nutrition Research, 55*, 1–99.

Clarkson PM, Hubal MJ. (2002). Exercise-induced muscle damage in humans. *American Journal of Physical Medicine and Rehabiliation, 81*(11 Suppl.), S52-S69.

Clarkson PM, Newham DJ. (1995). Associations between muscle soreness, damage, and fatigue. *Advances in Experimental Medicine and Biology, 384*, 457-469.

Cockburn E, Bell, PG, Stevenson E. (2013). Effect of milk on team sport performance following exercise induced muscle damage. *Medicine and Science in Sports and Exercise,*(Epub ahead of print).

Corbit R, Ebbs S, King ML, Murphy LL. (2006). The influence of lead and arsenite on the inhibition of human breast cancer MCF-7 cell proliferation by American ginseng root (Panax quinquefolius L.) *Life Sciences, 78*(12), 1336–1340.

Corona BT, Balog EM, Doyle JA, Rupp JC, Luke RC, Ingalls CP. (2010). Junctophilin damage contributes to early strength deficits and EC coupling failure after eccentric contractions. *American Journal of Physiology- Cell Physiology, 298*(2), C365-376,

Court WE. (1975). Ginseng: a Chinese folk medicine of current interest. *Pharmaceutical Journal, 214*, 180-181.

Court WE. Ginseng: The history of an insignificant plant. *Pharmaceutical Historian, 30*(3), 38-44.

Cui JF. (1995). Identification and quantification of ginsenosides in various commercial ginseng preparations. *European Journal Pharmaceutical Sciences, 3*(2), 77-85.

Dascalu A, Sievenpiper JL, Jenkins AL, Stavro MP, Leiter LA, Arnason T, Vuksan V. (2007). Five batches representative of Ontario-grown American ginseng root produce comparable reductions of postprandial glycemia in healthy individuals. *Canadian Journal Physiology and Pharmacology*, *85*(9), 856–864.

Davydov M, Krikorian AD. (2000). Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *Journal of Ethnopharmcology, 72*(3), 345-393.

de Vries JHM, Zock PL, Mensink RP, Katan MB. (1994). Underestimation of energy intake by 3-d records compared with energy intake to maintain body weight in 269 nonobese adults. *The American Journal of Clinical Nutrition,60*(6), 855-860.

Deschenes, MR, Brewer RE, Bush JA, McCoy RW, Volek JS, & Kraemer WJ. (2000). Neuromuscular disturbance out lasts other symptoms of exercise-induced muscle damage. *Journal of the Neurological Sciences, 174*(2), *92–99.*

Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan CS. (2003). Anti-hyperglycemic effects of ginseng: comparison between root and berry. *Phytomedicine,* 10(6-7), 600–605.

Dharmananda S. (2002). The nature of ginseng: traditional use, modern research, and the question of dosage. *HerbalGram*, (54), 34–51.

Dickman JR, Koenig RT, Ji LL. (2009). American ginseng supplementation induces an oxidative stress in postmenopausal women. *Journal of the American College of Nutrition, 28*(2), 219-228.

Donovan JL, DeVane LC, Chavin KD, Taylor RM, Markowitz JS. (2003). Siberian ginseng (Eleutheroccus senticosus) effects on CYP2D6 and CYP3A4 activity in normal volunteers. *Drug Metabolism and Disposition: The Biological Fate of Chemicals, 31*(5), 519-522.

Duda RB, Kang SS, Archer SY, Meng S, Hodin RA. (2001). American ginseng transcriptionally activates p21 mRNA in breast cancer cell lines. *Journal of Korean Medical Science, 16* (Suppl), S54–60.

Duda RB, Zhong Y, Navas V, Li MZ, Toy BR, Alavarez JG. (1999). American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 breast cancer cell growth. *Journal of Surgical Oncology, 72*(4), 230–239.

Ellingwood F. (1915). *American materia medica, therapeutics and pharmacognosy*. Chicago.

Elyakov GB, Strigina LI, Uvarova NI, Vaskovsky VE, Dzizenko AK, Kochetkov NK. (1964). Glycosides from ginseng roots. *Tetrahedron Letters, 5*(48), 3591-3597.

Estaki M, Noble EG. (2012). Differences in alcohol versus aqueous extracts of North American Ginseng in protecting against eccentric exercise-induced muscle damage in rats. *Journal of the Federation of American Societies for Experimental Biology, 26*, 1141.5.

Eston RG, Critchley N, Baltzopoulos V. (1994). Delayed-onset muscle soreness, strength loss characteristics and creatine kinase activity following uphill and downhill running. *Journal of Sports Sciences, 12,* 135.

Eston RG, Lemmey AB, McHugh MP, Byrne C, Walsh SE. (2000). Effect of stride length on symptoms of exercise induced muscle damage during a repeated bout of downhill running. *Scandinavian Journal of Medicine and Science in Sports, 10*(4), 199-204.

Farr T, Nottle C, Nosaka K, Sacco P. (2002). The effects of therapeutic massage on delayed onset muscle soreness and muscle function following downhill walking. *Journal of Science and Medicine in Sport*, *5*(4), 297-306.

Fielding RA, Violan MA, Svetkey L, Abad LW, Manfredi TJ, Cosmas A, Bean J. (2000). *Medicine and Science in Sports and Exercise, 32*(2), 359-364.

Flann KL, LaStayo PC, McClain DA, Hazel M, Lindstedt SL. (2011). Muscle damage and muscle remodeling: no pain, no gain? *The Journal of Experimental Biology, 214*(Pt 4), 674-679.

Flower RJ. (1990). Lipocortin. *Progress in Clinical and Biological Research, 349*, 11-25.
Foley JM, Jayaraman RC, Prior BM, et. al. (1999). MR measurements of muscle damage and adaptation after eccentric exercise. *Journal of Applied Physiology, 87*(6), 2311–2318.

Fournier AR, Proctor JTA, Gauthier L, Khanizadeh S, Belanger A, Gosselin A, Dorais M. (2003). Understory light and root ginsenosides in forest-grown Panax quinquefolius. *Phytochemistry, 63*(7), 772-782.

Friden J, Lieber RL. (2001). Eccentric exercise-induced injuries to contractile and cytoskeletal muscle fiber components. *Acta Physiologica Scandinavica, 171*(3), 321-326.

Fröhlich M, Faude O, Klein M, Pieter A, Emrich E, Meyer T. (2014). Strength training adaptations after cold water immersion. *The Journal of Strength and Conditioning Research,* epub ahead of print.

Fu Y, Ji LL. (2003). Chronic ginseng consumption attenuates age-associated oxidative stress in rats. *The Journal of Nutrition, 133*(11), 3603–3609.

Fuzzati N. (2004). Analysis methods of ginsenosides. *Journal of Chromatography B, 812*(1-2), 119–133.

Gillis CN. (1997). Panax ginseng pharmacology: a nitric oxide link? *Biochemical Pharmacology, 54*(1), 1-8.

Goldstein B. (1975). Ginseng: its history, dispersion, and folk tradition. *The American Journal Chinese Medicine, 3*(3), 223–234.

Grandhi A, Mujumdar AM, Patwardhan B. (1994). A comparative pharmacological investigation of Ashwagandha and ginseng. *Journal of Ethnopharmacology, 44(3), 131-135.*

Gribaudo CG, Ganzit GP, Biancotti PP, Astegiano P. (1991). Effetti della somministrazione di un prodotto naturale ergogenico sulle doti aerobiche di ciclisti agonisti. *Medicina Dello Sport, 44*(4)*,* 335-43.

Gribaudo CG, Ganzit GP, Verzini EF. (1990). Effetti sulla forza e sulla fatica muscolare di un prodotto ergogenico di origine naturale. *Medicina Dello Sport, 43*(4), 241-249.

Han KL, Jung MH, Sohn JH, Hwang JK. (2006). Ginsenoside 20(S)-protopanaxatriol (PPT) activates peroxisome proliferator-activated receptor gamma (PPAR gamma) in 3T3-L1 adipocytes. *Biological and Pharmaceutical Bulletin, 29*(1), 110–113.

Han M, Fang XL. (2006). Difference in oral absorption of ginsenoside Rg1 between in vitro and in vivo models. *Acta Pharmacologica Sinica, 27*(4), 499-505.

Han M, Fu S, Gao JQ, Fang XL. (2009). Evaluation of intestinal absorption of ginsenoside Rg1 incorporated in microemulison using parallel artificial membrane permeability assay. *Biological and Pharmaceutical Bulletin, 32*(6), 1069-1074.

Han M, Sha X, Wu Y, Fang X. (2006). Oral absorption of ginsenoside Rb1 using in vitro and in vivo models. *Planta Medica, 72*(5), 398-404.

Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. (2001). Variability in commercial ginseng products: an analysis of 25 preparations. *The American Journal of Clinical Nutrition, 73*(6), 1101-1106.

Helms, S. (2004). Cancer prevention and therapeutics: Panax ginseng. *Alternative Medicine Review: A Journal of Clinical Therapeutic, 9*(3), 259-274.

Hilbert JE, Sforzo GA, Swensen T. (2003). The effects of massage on delayed onset muscle soreness. *British Journal of Sports Medicine*, *37*(1), 72-75.

Hofseth LJ, Wargovich MJ. Inflammation, cancer, and targets of ginseng. (2007). *The Journal of Nutrition, 137*(1 Suppl.), 183S-185S.

Howatson G, Van Someren KA. (2007). Evidence of a contralateral repeated bout effect after maximal eccentric contractions. *European Journal of Applied Physiology, 101*(2), 207-214.

Hsu CC, Ho MC, Lin LC, Su B, Hsu MC. (2005). American ginseng supplementation attenuates creatine kinase level induced by submaximal exercise in human beings. *World Journal of Gasteroenterology, 11*(34), 5327-5331.

Hu SY. (1976). The genus Panax (ginseng) in Chinese medicine. *Economic Botany, 30*(1), 11-28.

Hu SY. (1977). A contribution to our knowledge of ginseng. *The American Journal Chinese Medicine, 5*(1), 1–23

Ivy JL, Katz AL, Cutler CL, Sherman WM, Coyle EF. (1988). Muscle glycogen synthesis after exercise: effect of time of carbohydrate ingestion. *The Journal of Applied Physiology,64*(4), 1480-1485.

Jia L, Zhao Y. (2009). Current evaluation of the millennium phytomedicine--ginseng (I): etymology, pharmacognosy, phytochemistry, market and regulations. *Current Medicinal Chemistry, 16*(19), 2475–2484.

Jia WW, Bu X, Philips D, Yan H, Liu G, Chen X, Bush JA, Li G. (2004). Rh2, a compound extracted from ginseng, hypersensitizes multidrug-resistant tumor cells to chemotherapy. *Canadian Journal of Physiology and Pharmacology, 82*(7), 431–437.

Jiang HP, Qiu YK, Cheng DR, Kang TG, Dou DQ. (2008). Structure elucidation and complete NMR spectral assignments of two new dammarane-type tetraglycosides from Panax quinquefolium. *Magnetic Resonance in Chemistry, 46*(8), 786–790.

Jin Y, Hofseth AB, Cui XL, Windust AJ, Poudyal D, Chumanevich AA, Matesic LE, Singh NP, Nagarkatti M, Nagarkatti PS, Hofseth LJ. (2010). American ginseng suppresses colitis through

p53-mediated apoptosis of inflammatory cells. *Cancer Prevention Research (Philadelphia, Pa.),* 3(3), 339–347.

Joe EK, Schussheim AE, Longrois D, Mäki T, Kelly RA, Smith TW, Balligand JL. (1998). Regulation of cardiac myocyte contractile function by nitric oxide synthase (iNOS): mechanisms of contractile depression by nitric oxide. *Journal of Molecular and Cellular Cardiology, 30*(2), 303-315.

Joo SS, Won TJ, Lee DI. (2005). Reciprocal activity of Ginsenosides in the production of proinflarnmatory repertoire, and their potential roles in neuroprotection in vitro. *Planta Medica, 71*(5), 476–481.

Jung HL, Kwak HE, Kim SS, Kim YC. (2011). Effects of Panax ginseng supplementation on muscle damage and inflammation after uphill treadmill running in humans. *The American Journal of Chinese Medicine, 39*(3), 441-450.

Kamandulis S, Skurvydas A, Brazaitis M, Skikas L, Duchateau J. (2010). The repeated bout effect of eccentric exercise is not associated with changes in voluntary activation. *European Journal of Applied Physiology, 108*(6), 1065- 1074.

Karikura M, Miyase T, Tanizawa H, Takino Y, Taniyama T, Hayashi T. (1990). Studies on absorption, distribution, excretion and metabolism of ginseng saponins. V. The decomposition products of ginsenoside Rb2 in the large intestine of rats. *Chemical and Pharmaceutical Bulletin,* 38(10), 2859-2861.

Kasai R, Besso H, Tanaka O, Saruwatari Y, Fuwa T. (1983). Saponins of red ginseng. *Chemical and Pharmaceutical Bulletin, 31*(6), 2120–2125.

Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. (2002). Recent patterns of medication use in the ambulatory adult population of the United States: The slone survey. *The Journal of the American Medical Association, 287*(3), 337–344.

Keum, YS, Park KK, Lee JM, Chun KS, Park JH, Lee SK, Kwon HJ, Surh YJ. (2000). Antioxidant and antitumor promoting activities of the methanol extract of heat-processed ginseng. *Cancer Letters, 150*(1), 41–48.

Kim SK, Sakamoto I, Morimoto K, Sakata M, Yamasaki K, Tanaka O. (1981). Seasonal variation of saponins, sucurose and monosaccharides in cultivated ginseng roots. *Planta Medica, 42*(6), 181-186.

Kim WY, Kim JM, Han SB, Lee SK, Kim ND, Park MK, Kim CK, Park JH. (2000). Steaming of ginseng at high temperature enhances biological activity. *Journal of Natural Products*, *63*(12), 1702–1704.

King J. (1878). *The American dispensatory: 11th edition.* Cincinnati, OH: Wilstach & Baldwin.

Koh TJ, Brooks SV. (2001). Lengthening contractions are not required to induce protection from contraction-induced muscle injury. *American Journal of Physiology- Regulatory, Integrative and Comparative Physiology, 281*(1), R155-R161.

Komulainen J, Takala TE, Vihko V. (1995). Does increased serum creatine kinase activity reflect exercise induced muscle damage in rats? *International Journal of Sports Medicine*, *16*(3), 150-154.

Kuipers, H. (1994). Exercise-induced muscle damage. *International Journal of Sports Medicine, 15*(3), 132-135.

Kwon SW, Han SB, Park IH, Kim JM, Park MK, Park JH. (2001). Liquid chromatographic determination of less polar ginsenosides in processed ginseng. *Journal of Chromatography A, 921*(2), 335-339.

Kwon SW, Han SB, Park IH, Kim JM, Park MK, Park JH. (2001). Liquid chromatographic determination of less polar ginsenosides in processed ginseng. *Journal of Chromatography A, 921*(2), 335–339.

Lau AJ, Seo BH, Woo SO, Koh HL. (2004). High-performance liquid chromatographic method with quantitative comparisons of whole chromatograms of raw and steamed Panax notoginseng. *Journal of Chromatography A*, *1057*(1-2), 141–149.

Lau WS, Chan RY, Guo DA, Wong MS. (2008). Ginsenoside Rg1 exerts estrogen-like activities via ligand-independent activation of ERalpha pathway. *The Journal of Steroid Biochemistry and Molecular Biology, 108*(1-2), 64–71.

Lauritzen F, Paulsen G, Raastad T, Bergersen LH, Owe SG. (2009). Gross ultrastructural changes and necrotic fiber segments in elbow flexor muscles after maximal voluntary eccentric action in humans. *Journal of Applied Physiology, 107*(6), 1923-1934.

Leahy DT & Pintauro SJ. (2013). Branched-chain amino acid Plus glucose supplement reduces exercise-induced delayed onset muscle soreness in college-age females. *International Scholarly Research Notices, 2013*, article ID: 921972, 5 pages.

LeBlanc AD, Jaweed M, & Evans H. (1993). Evaluation of muscle injury using magnetic resonance imaging. *Clinical Journal of Sport Medicine, 3*(1), 26–30.

Lee WK, Kao ST, Liu IM, Cheng JT. (2006). Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in wistar rats. *Clinical and Experimental Pharmacology and Physiology, 33*(1-2), 27–32.

Leung KW, Cheung LW, Pon YL, Wong RN, Mak NK, Fan TP, Au SC, Tombran-Tink J, Wong AS. (2007). Ginsenoside Rb1 inhibits tube-like structure formation of endothelial cells by

regulating pigment epithelium-derived factor through the oestrogen beta receptor. *British Journal of Pharmacology, 152*(2), 207–15.

Li BH, Wang CZ, He TC, Yuan CS, Du W. (2010). Antioxidants potentiate American ginseng-induced killing of colorectal cancer cells. *Cancer Letters, 289*(1), 62–70.

Li CP, Li RC. (1973). An introductory note to ginseng. *The American Journal of Chinese Medicine, 1*(2), 249-261.

Li SH, Chu Y. (1999). Anti-inflammatory effects of total saponins of Panax notoginseng. *Acta Pharmacologica Sinica, 20*(6), 551-554.

Li TSC, Mazza G, Corttrell AC, Gao L. (1996). Ginsenosides in roots and leaves of American ginseng. *Journal of Agricultural Food Chemistry, 44*(3), 717-720.

Li TSC, Mazza G. (1999). Correlations between leaf and soil mineral concentrations and ginsenoside contents in American ginseng. *Hortscience, 34*(1), 85-87.

Li TSC, Wardle D. (2002). Seasonal fluctuations of leaf and root weight and ginsenoside contents of 2-, 3-, and 4 year-old American ginseng plants. *HortTechnology, 12*(2), 229-232.

Li TSC. (1995). Asian and American ginseng—A review. *HortTechnology, 5*(1), 27–34.

Liao B, Newmark H, Zhou R. (2002). Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. *Experimental Neurology*, *173*(2), 224–234.

Liberti LE, Der Marderosian A. (1978). Evaluation of commercial ginseng products. *Journal of Pharmaceutical Sciences, 67*(10), 1487-1489.

Lieber RL, Friden J. (1993). Muscle damage is not a function of muscle force but active muscle strain. *Journal of Applied Physiology, 74*(2), 520-526.

Lightfoot, T Char D, McDermott J, Goya C. (1997). Immediate post exercise massage does not attenuate delayed onset muscle soreness. *Journal of Strength & Conditioning Research, 11*(2), 119-124.

Lim W, Mudge KW, Vermeylen F. (2005). Effects of population, age, and cultivation methods on ginsenoside content of wild American ginseng (Panax quinquefolium). *Journal of Agricultural and Food Chemistry, 53*(22), 8498–8505.

Lin WN, Lu HY, Lee MS, Yang SY, Chen HJ, Chang YS, Chang WT. (2010). Evaluation of the cultivation age of dried ginseng radix and its commercial products by using (1)H-NMR fingerprint analysis. *The American Journal of Chinese Medicine, 38*(1), 205–218.

Liu CX, Xiao PG. (1992). Recent advances in ginseng research in China. *Journal of Ethnopharmacology, 36*(1), 27–38.

Liu ZJ, Zhao M, Zhang Y, Xue JF, Chen NH. (2010). Ginsenoside Rg1 promotes glutamate release via a calcium/calmodulin-dependent protein kinase II-dependent signaling pathway. *Brain Research, 1333,* 1-8.

Lü JM, Yao Q, Chen C. (2009). Ginseng compounds: an update on their molecular mechanisms and medical applications. *Current Vascular Pharmacology, 7*(3), 293-302.

Lund H, Søndergaard K, Zachariassen T, Christensen R, Bülow P, Henriksen M, Bartels EM, Danneskiold-Samsøe B, Bliddal H. (2005) Learning effect of isokinetic measurements in healthy subjects, and reliability and comparability of Biodex and Lido dynamometers. *Clinical Physiology and Functional Imaging, 25*(2), 75-82.

Magal M, Dumke CL, Urbiztondo ZG, Cavill MJ, Triplett NT, Quindry JC, McBride JM, Epstein Y. (2010). Relationship between serum creatine kinase activity following exercise-induced muscle damage and muscle fibre composition. *Journal of Sport Sciences, 28*(3), 257-266.

Maimer A, Remppis A, Sack FU, Ringes-Lichtenburg, Greten T, Brazkiewicz F, Schröder S, Goncalves M, Efferth T, Greten HJ. (2013). Objectifying acupuncture effects by lung function and numeric rating scale in patients undergoing heart scale. *Evidence-Based Complementary and Alternative Medicine, 2013*, Article ID 219817.

Mair J, Koller A, Artner-Dworzak E, Haid C, Wicke K, Judmaier W, Puschendorf B. (1992). Effects of exercise on plasma myosinheavy chain fragments and MRI of skeletal muscle. *Journal of Applied Physiology, 72*(2), 656–663.

Mair J, Mayr M, Müller E, Koller A, Haid C, Artner-Dworzak E, Calzolari C, Larue C, Puschendorf B. (1995). Rapid adaptation to eccentric exercise-induced muscle damage. *International Journal of Sports Medicine, 16*(6), 352-356.

Mancinelli, CA, Davis DS, Aboulhosn L, Eisenhofer J, Foutty S. (2006). The effects of massage on delayed onset muscle soreness and physical performance in female collegiate athletes. *Physical Therapy in Sport*, *7*(1), 5-13.

Matsuda H, Namba K, Fukuda S, Tani T, Kubo M. (1986). Pharmacological study on Panax ginseng C.A. Meyer: III. Effects of red ginseng on experimental disseminated intravascular coagulation. (2). Effects of ginsenosides on blood coagulative and fibrinolytic systems. *Chemical and Pharmaceutical Bulletin, 34*(3), 1153-1157.

McArdle F, Spiers S, Aldemir H, Vasilaki A, Beaver A, Iwanejko L, McArdle A, Jackson MJ. (2004). Preconditioning of skeletal muscle against contraction induced damage: the role of adaptations to oxidants in mice. *Journal of Physiology, 561*(Pt 1), 233-244.

McBride JM, Kraemer WJ, Triplett-McBride T, Sebastianelli W. (1998). Effect of resistance exercise on free radical production. *Medicine and Science in Sports and Exercise, 30*(1), 67-72.

McHugh MP. (2003). Recent advances in the understanding of the repeated bout effect: the protective effect against muscle damage from a single bout of eccentric exercise. *Scandinavian Journal of Medicine and Science in Sports, 13*(2), 88-97.

McHugh MP, Connely DA, Eston RG, Gleim GW. (1999). Exercise-induced muscle damage and potential mechanisms for the repeated bout effect. *Sports Medicine, 27*(3), 157-170.

McNaughton L, Egan G, Caelli G. (1989). A comparison of Chinese and Russian ginseng as ergogenic aids to improve various facets of physical fitness. *International Clinical Nutrition Review*, 9(1), 32-35.

Mehendale S, Aung H, Wang A, Yin JJ, Wang CZ, Xie JT, Yuan CS. (2005). American ginseng berry extract and ginsenoside Re attenuate cisplatin-induced kaolin intake in rats. *Cancer Chemotherapy and Pharmacology, 56*(1), 63–69.

Mickleborough TD. (2013). Omega-3 polyunsaturated fatty acids in physical performance optimization. *International Journal of Sport Nutrition and Exercise Metabolism, 23*(1), 83-96.

Minetto M, Rainoldi A, Gazzoni M, Terzolo M, Borrione P, Termine A, Saba L, Dovio A, Angeli A, Paccotti P. (2005). Differential responses of serum and salivary interleukin-6 to acute strenuous exercise. *European Journal of Applied Physiology, 93*(5-6), 679–686.

Miller LG. (1998). Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Archives of Internal Medicine, 158*(20), 2200-2211.

Miyama M, Nosaka K. (2004). Muscle damage and soreness following repeated bouts of consecutive drop jumps. *Advances in Exercise and Sports Physiology, 10*(3), 63-69.

Mohaupt MG, Karas RH, Babiychuk EB, Sanchez-Freire V, Monastyrskaya K, Iyer L, Hoppeler H, Breil F, Draeger A. (2009). Association between statin-associated myopathy and skeletal muscle damage. *Canadian Medical Association Journal, 181*(1-2), E11-E18.

Moore DR, Young M, Phillips SM. (2012). Similar increases in muscle size and strength in young men after training with maximal shortening or lengthening contractions when matched for total work. *European Journal of Applied Physiology, 112*(4), 1587-1592.

Mudge K, Lim W, Lardner J, Jousselin V. (2001). Ginsenosides as quality indicators in woods-grown American ginseng. Department of Horticulture, Cornell University, Ithaca, New York, USA.

Nah SY, Kim DH, Rhim H. (2007). Ginsenosides: Are any of them candidates for drugs acting on the central nervous system? *CNS Drug Reviews,* 13(4), 381–404.

Nah SY. (1997). Ginseng: Recent advances and trends. *Korean Journal of Ginseng Science*, *21*(1), 1-12.

Nakamura S, Sugimoto S, Matsuda H, Yoshikawa M. (2007) Medicinal flowers. XVII. New dammarane-type triterpene glycosides from flower buds of American ginseng, Panax quinquefolium L. Chemical and Pharmaceutical Bulletin, 55(9), 1342–1348.

Newham DJ, Jones DA, Clarkson PM. (1987). Repeated high force eccentric exercise: effects on muscle pain and damage. *Journal of Applied Physiology, 63*(4), 1381-1386.

Newham DJ, McPhail G, Mills KR, Edwards RH. (1983). Ultrastructural changes after concentric and eccentric contractions of the human muscle. *Journal of the Neurological Sciences, 61*(1), 109-122.

Ng CC, Ng YK. (1986). The effect of ginseng: a traditional Chinese medicine on physical capacity [abstract]. *The XXIII FIMS World Congress of Sports Medicine Abstracts 1986 (Champaign, IL), Fédération Internationale de Médicine Sportive,* 196.

Nissen S, Sharp R, Ray M, Rathmacher JA, Rice D, Fuller JC Jr., Connelly AS, Abumrad N. (1996). Effect of leucine metabolite beta-hydroxy-beta-methylbutyrate. *Journal of Applied Physiology, 81*(5), 2095-2104.

Nosaka K, Aoki MS. (2011). Repeated bout effect: research update and future perspective. *Brazilian Journal of Biomotricity, 5*(1), 5-15.

Nosaka K, Clarkson PM. (1996). Changes in indicators of inflammation after eccentric exercise of the elbow flexors. *Medicine and Science in Sports Exercise, 28*(8), 953–961.

Nosaka K, Clarkson PM, McGuiggin ME, Byrne JM. (1991). Time course of muscle adaptation after high force eccentric exercise. *European Journal of Applied Physiology* and *Occupational Physiology, 63*(1), 70-76.

Nosaka K, Sakamoto K, Newton M, Sacco P. (2001). How long does the protective effect on eccentric exercise-induced muscle damage last? *Medicine and Science in Sports and Exercise, 33*(9), 1490-1495.

Nosaka K. (2008). Muscle soreness, muscle damage and repeated bout effect. In: Tiidus PM (Eds.), *Skeletal muscle damage and repair* (59-76). Champaign, IL: Human Kinetics.

Nosaka K. (2010). Exercise-induced muscle damage and delayed onset muscle soreness. In: Cardinale M, Newton R, Nosaka K (Eds.), *Strength and conditioning: biological principals and practical applications* (179-192). Chichester, West Sussex, UK: Wiley-Blackwell.

Nunan D, Howatson G, van Someren, KA. (2010). Exercise-Induced muscle damage is not attenuated by [beta]-hydroxy-[beta]-methylbutyrate and [alpha]-ketoisocaproic acid supplementation. *Journal of Strength and Conditioning Research, 24*(2), *531-537.*

Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. (1999). Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *The Journal of Physiology, 515*(Pt 1), 287–291.

Paulsen G, Cumming KT, Holden G, Hallén J, Rønnestad BR, Sveen O, Skaug A, Paur I, Bastani NE, Østgaard HN, Buer C, Midttun M, Freuchen F, Wiig H, Ulseth ET, Garthe I, Blomhoff R, Benestad HB, Raastad T. (2014). Vitamin C and E supplementation hampers cellular adaptation to endurance training in humans: a double-blind randomized controlled trial. *The Journal of Physiology,*(Epub ahead of print).

Pamplona R, Portero-Otin M, Requena JR, Thorpe SR, Herrero A, Barja G. (1999). A low degree of fatty acid unsaturation leads to low lipid peroxidation lipoxidation-derived protein modification in heart mitochondria of the longeous pigeon than in the short-lived rat. *Mechanisms of Ageing and Development, 106*(3)*,* 283–*296.*

Papapetropoulos A. (2007). A ginseng-derived oestrogen receptor beta (ERbeta) agonist, Rb1 ginsenoside, attenuates capillary morphogenesis. *British Journal of Pharmacology, 152*(2), 172–174.

Park JA, Lee KY, Oh YJ, Kim KW, Lee SK. (1997). Activation of caspase-3 protease via a Bcl-2-insensitive pathway during the process of ginsenoside Rh2-induced apoptosis. *Cancer Letters, 121*(1), 73–81.

Park S, Ahn IS, Kwon DY, Ko BS, Jun WK. (2008). Ginsenosides Rb1 and Rg1 suppress triglyceride accumulation in 3T3-L1 adipocytes and enhance beta-cell insulin secretion and viability in Min6 cells via PKA-dependent pathways. *Bioscience, Biotechnology, and Biochemistry, 72*(11), 2815–2823.

Pedersen BK, Ostrowski K, Rohde T, Bruunsgaard H. (1998). The cytokine response to strenuous exercise. *Canadian Journal of Physiology and Pharmacology, 76*(5), 505–511.

Perez AC, Cabral de Oliveira AC, Prieto JG, Ferrando A, Vila L, Alvarez AI. (2002). Quantitative assessment of nitric oxide in rat skeletal muscle and plasma after exercise. *European Journal of Applied Physiology, 88*(1-2), 189-191.

Perry LM, Metzger J. (1980). *Medicinal plants of east and southeast Asia: Attributed properties and uses.* Cambridge, MA: MIT Press.

Peternelj TT, Coombes JS. (2011). Antioxidant supplementation during exercise training: beneficial or detrimental? *Sports Medicine, 41*(12), 1043-1069.

Pharand C, Ackman ML, Jackevicius CA, Paradiso-Hardy FL, Pearson GJ. (2003). Use of OTC and herbal products in patients with cardiovascular disease. *The Annals Pharmacotherapy*, *37*(6), 899–904.

Phillipson JD, Anderson LA. (1984). Ginseng: quality, safety, and efficacy? *Pharmaceutical Journal, 232*, 161-165.

Piltch A, Sun L, Fava RA, Hayashi J. (1989). Lipocortin-independent effect of dexamethasone on phospholipase activity in a thymic epithelial cell line. *The Biochemical Journal, 261*(2), 395-400.

Pizza FX, Koh TJ, McGregor SJ, Brooks SV. (2002). Muscle inflammatory cells after passive stretches, isometric contractions, and lengthening contractions. *Journal of Applied Physiology, 92*(5), 1873-1878.

Popov IM, Goldwag WJ. (1973). A review of the properties and clinical effects of ginseng. *The American Journal of Chinese Medicine, 1*(2), 263-270.

Qi LW, Wang CZ, Yuan CS. (2010). American ginseng: Potential structure-function relationship in cancer chemoprevention. *Biochemical Pharmacology, 80*(7), 947–954.

Qi LW, Wang CZ, Yuan CS. (2011). Ginsenosdies from American ginseng: Chemical and pharmacological diversity. *Phytochemistry, 72*(8), 689-699.

Qiu YK, Dou DQ, Cai LP, Jiang HP, Kang TG, Yang BY, Kuang HX, Li MZC. (2009). Dammarane-type saponins from Panax quinquefolium and their inhibition activity on human breast cancer MCF-7 cells. *Fitoterapia,* 80(4), 219–222.

Qu CL, Bai YP, Jin XQ, Wang YT, Zhang K, You JY, Zhang HQ. (2009). Study on ginsenosides in different parts and ages of Panax quinquefolius L. *Food Chemistry,* 115(1), 340–346.

Qu CL, Bai YP, Jin XQ, Wang YT, Zhang K, You JY, Zhang HQ. (2009). Study on ginsenosides in different parts and ages of Panax quinquefolius L. *Food Chemistry, 115*(1), 340–346.

Raastad T, Owe SG, Paulsen G, Enns D, Overgaard K, Crameri R, Kill S, Belcastro A, Bergersen L, Hallén J. (2010). Changes in calpain activity, muscle structure, and function after eccentric exercise. *Medicine and Science in Sports and Exercise, 42*(1), 86-95.

Radad K, Gille G, Liu LL, Rausch WD. (2006). Use of ginseng in medicine with emphasis on neurodegenerative disorders. *Journal of Pharmacological Sciences, 100*(3), 175–186.

Radad K, Gille G, Moldzio R, Saito H, Rausch WD. (2004). Ginsenosides Rb-1 and Rg(1) effects on mesencephalic dopaminergic cells stressed with glutamate. *Brain Research, 1021*(1), 41–53.

Rausch WD, Liu S, Gille G, Radad K. Neuroprotective effects of ginsenosides. (2006). *Acta Neurobiologiae Experimentalis, 66*, 369–375.

Reid MB. (1998). Role of nitric oxide in skeletal muscle: synthesis, distribution and functional importance. *Acta Physiologica Scandinavica, 162*(3), 401-409.

Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, Stumvoll, M, Kahn RC, Blüher M. (2009). Antioxidants prevent health-promoting effects of physical exercise in humans. *Proceeding of the National Academy of Sciences of the United States of America, 106*(21), 8665-8870.

Rodenburg JB, de Boer RW, Schiereck P, van Echteld CJ, & Bar PR. (1994). Changes in phosphorus compounds and water content in skeletal muscle due to eccentric exercise. *European Journal of Applied Physiology and Occupational Physiology, 68*(3), *205–213.*

Roig M, O'Brien K, Kirk G, Murray R, McKinnon P, Shadgan B, Reid WD. (2009). The effects of eccentric versus concentric resistance training on muscle strength and mass in healthy adults: a systematic review with meta-analysis. *British Journal of Sports Medicine, 43*(8), 556-568.

Ryu SJ, Chien YY. (1995). Ginseng-associated cerebral arteritis. *Neurology, 45*(4), 829–830.

Schlag EM, McIntosh MS. (2006). Ginsenoside content and variation among and within American ginseng (Panax quinquefolius L.) populations. *Phytochemistry, 67*(14), 1510–1519.

Scholey A, Ossoukhova A, Owen L, Ibarra A, Pipingas A, He K, Roller M, Stough C. (2010). Effects of American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study. *Psychopharmacology, 212*(3), 345–356.

Sellwood KL, Brukner P, Williams D, Nicol A, Hinman R. (2007). Ice-water immersion and delayed-onset muscle soreness: a randomised controlled trial. *British Journal of Sports Medicine, 41*(6), 392-997.

Sengupta S, Toh SA, Sellers LA, Skepper JN, Koolwijk P, Leung HW, Yeung HW, Wong RNS,

Sasisekharan R, Fan TPD. (2004). Modulating angiogenesis - The yin and the yang in ginseng. *Circulation, 110*(10), 1219–1225.

Shang W, Yang Y, Jiang B, Jin H, Zhou L, Liu S, Chen M. (2007). Ginsenoside Rb1 promotes adipogenesis in 3T3-L1 cells by enhancing PPARgamma2 and C/EBPalpha gene expression. *Life Sciences,* 80(7), 618–625.

Shang W, Yang Y, Zhou L, Jiang B, Jin H, Chen M. (2008). Ginsenoside Rb1 stimulates glucose uptake through insulin-like signaling pathway in 3T3-L1 adipocytes. *The Journal of Endocrinology, 198*(3), 561–569.

Shao ZH, Xie JT, Vanden Hoek TL, Mehendale S, Aung H, Li CQ, Qin Y, Schumacker PT, Becker LB, Yuan CS. (2004). Antioxidant effects of American ginseng berry extract in cardiomyocytes exposed to acute oxidant stress. *Biochimica et Biophysica Acta, 1670*(3), 165–171.

Shellock FG, Fukunaga T, Mink JH, & Edgerton VR. (1991). Exertional muscle injury: evaluation of concentric versus eccentric actions with serial MR imaging. *Radiology, 179*(3), 659–664.

Shimomura Y, Yamamoto Y, Bajotto G, Sato J, Murakami T, Shimomura N, Kobayashi H, Mawatari K. (2006). Nutraceutical effects of branched-chain amino acids on skeletal muscle. *The Journal of Nutrition, 136*(2), 529S-532S.

Shin YW, Bae EA, Kim DH. (2006). Inhibitory effect of ginsenoside Rg5 and its metabolite ginsenoside Rh3 in an oxazolone-induced mouse chronic dermatitis model. *Archives of Pharmacal Research,* 29(8), 685–690.

Sievenpiper JL, Arnason JT, Leiter LA, Vuksan V. (2004). Decreasing, null and increasing effects of eight popular types of ginseng on acute postprandial glycemic indices in healthy humans: the role of ginsenosides. *Journal of the American College of Nutrition, 23*(3), 248–258.

Sievenpiper JL, Arnason JT, Vidgen E, Leiter LA, Vuksan V. (2004). A systematic quantitative analysis of the literature of the high variability in ginseng (Panax spp.): should ginseng be trusted in diabetes? *Diabetes Care, 27*(3), 839–840.

Smith L, Keating M, Holbert D, Spratt D, McCammon M, Smith S. (1994). The effects of athletic massage on delayed onset of muscle soreness, creatine kinase, and neutrophil count: a preliminary report. *Journal of Orthopaedic and Sports Physical Therapy*, *19*(2), 93-99.

Soldati F, Tanaka O. (1984). Panax ginseng: relation between age of plant and content of ginsenosides. *Planta Medica, 50*(4), 351-352.

Street B, Byrne C, Eston R. (2011). Glutamine supplementation in recovery from eccentric exercise attenuates strength loss and muscle soreness. *Journal of Exercise Science and Fitness, 9*(2), 116-122.

Sun S, Qi LW, Du GJ, Mehendale SR, Wang CZ, Yuan CS. (2011). Red notoginseng: higher ginsenoside content and stronger anticancer potential than Asian and American ginseng. *Food Chemistry*, *125*(4), 1299–1305.

Takahashi H, Kuno S, Miyamoto T, Yoshioka H, Inaki M, Akima H, Katsuta S, Anno I, Itai Y. (1994). Changes in magnetic resonance images in human skeletal muscle after eccentric exercise. *European Journal of Applied Physiology and Occupational Physiology, 69*(5), 408-413.

Takino Y. (1994). Studies on pharmacodynamics of ginsenoside-Rg1, Rb1 and - Rb2 in rats. *Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan, 114*(8), 550-564.

Talbot JA, Morgan DL. (1998). The effects of stretch parameters on eccentric exercise-induced damage to toad skeletal muscle. *Journal of Muscle Cell Research and Cell Motility, 19*(3), 237-245.

Thiebaud RS. (2012). Exercise induced muscle damage: is it beneficial or detrimental? *Journal of Trainology, 1*(2), 36-44.

Tian J, Fu F. (2006). Neuroprotective effects of 20(S)-ginsenoside Rg3 on dopamine levels in the 6-hydroxydopamine lesioned mouse brain. *Movement Disorders, 21*, S76–S76.

Tian Y, Guo H, Han J, Guo D. (2005). Microbial transformation of 20(S)-protopanaxatriol by Mucor spinosus. *Journal of Natural Products, 68*(5), 678–680.

Tidball JG, Villalta SA. (2010). Regulatory interactions between muscle and the immune system during muscle regeneration. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 298*(5), R1173-1187.

Torres R, Ribeiro F, Duarte JA, Cabri JMH. (2012). Evidence of the physiotherapeutic interventions used currently after exercise-induced muscle damage: Systematic review and meta-analysis. *Physical Therapy in Sport, 13*(2), 101-114.

Van der Meulen JH, Kuipers H. & Drukker J. (1991). Relationship between exercise-induced muscle damage and enzyme release in rats. *Journal of Applied Physiology (Bethesda, Md.)*, 71(3), 999-1004.

Vina J, Sastre J, Pallardo FV, Gambini J, Borras C. (2006). Role of mitochondrial oxidative stress to explain the different longevity between genders: protective effect of estrogens. *Free Radical Research, 40*(12), 1359-1365.

Voces J, Cabral de Oliveira AC, Prieto JG, Villa L, Perez AC, Duarte IDG, Alvarez AI. (2004). Ginseng administration protects skeletal muscle from oxidative stress induced by acute exercise in rats. *Brazilian Journal of Medical and Biological Research, 37*(12), 1863-1871.

Vogler BK, Pittler MH, Ernst E. (1999). The efficacy of ginseng: a systematic review of randomized clinical trials. *European Journal of Clinical Pharmacology,55*(8), 567-575.

Volek JS, Kraemer WJ, Rubin MR, Gomez AL, Ratamess NA, Gaynor P. (2002). L-carnitine L-tartrate supplementation favorably affects markers of recovery from exercise stress. *American Journal of Physiology- Endocrinology and Metabolism, 282*(2), E474-E482.

Vuksan V, Sievenpiper JL, Xu Z, Wong EYY, Jenkins AL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Stavro MP. (2001). Konjac-mannan and American ginsing: Emerging alternative

therapies for type 2 diabetes mellitus. *Journal of the American College of Nutrition, 20*(5 Suppl.), 370S–380S.

Vuksan V, Sievenpiper JL. (2005). Herbal remedies in the management of diabetes: Lessons learned from the study of ginseng. *Nutrition Metabolism and Cardiovascular Diseases,* 15(3), 149–160.

Vuksan V, Sievenpiper JL. (2005). Herbal remedies in the management of diabetes: Lessons learned from the study of ginseng. *Nutrition, Metabolism, and Cardiovascular Diseases, 15*(3), 149–160.

Vuksan V. (2007). The evaluation and standardization of ginseng and its components for blood pressure regulation (study proposal). Retrieved from http://clinicaltrials.gov/show/NCT00730951

Wang AB, Wang CZ, Wu JA, Osinski J, Yuan CS. (2005). Determination of major ginsenosides in Panax quinquefolius (American ginseng) using, high-performance liquid chromatography. *Phytochemical Analysis, 16*(4), 272–277.

Wang CZ, Aung HH, Ni M, Wu JA, Tong R, Wicks S, He TC, Yuan CS. (2007). Red American ginseng: ginsenoside constituents and antiproliferative activities of heat-processed Panax quinquefolius roots. *Planta Medica, 73*(7), 669–674.

Wang CZ, Aung HH, Ni M, Wu JA, Tong RB, Wicks S, He TC, Yuan CS. (2007). Red American ginseng: Ginsenoside constituents and antiproliferative activities of heat-processed Panax quinquefolius roots. *Planta Medica, 73*(7), 669–674.

Wang CZ, Li XL, Wang QF, Mehendale SR, Fishbein AB, Han AH, Sun S, Yuan CS. (2009) The mitochondrial pathway is involved in American ginseng-induced apoptosis of SW-480 colon cancer cells. *Oncology Reports, 21*(3), 577–584.

Wang CZ, Mehendale SR, Yuan CS. (2007). Commonly used antioxidant botanicals: Active constituents and their potential role in cardiovascular illness. The *American Journal of Chinese Medicine, 35*(4), 543–558.

Wang CZ, Yuan, CS. (2008). Potential role of ginseng in the treatment of colorectal cancer. *The American Journal of Chinese Medicine, 36*(6), 1019-1028.

Wang CZ, Zhang B, Song WX, Wang A, Ni M, Luo X, Aung HH, Xie JT, Tong R, He TC, Yuan CS. (2006). Steamed American ginseng berry: ginsenoside analyses and anticancer activities. *Journal of Agricultural and Food Chemistry, 54*(26), 9936–9942.

Wang CZ, Zhang B, Song WX, Wang AB, Ni M, Luo XJ, Aung HH, Xie JT, Tong R, He TC, Yuan CS. (2006). Steamed American ginseng berry: Ginsenoside analyses and anticancer activities. *Journal of Agricultural and Food Chemistry, 54*(26), 9936–9942.

Wang JX. (1987). The earliest officially published pharmacopeia in the world. *Journal of Traditional Chinese Medicine, 7*(2), 155-156.

Wang LCH, Lee T-F. (1998). Effect of ginseng saponins on exercise performance in non-trained rats. *Planta Medica, 64*(2), 130-113.

Wang LCH, Lee T-F. (1998). Effect of ginseng saponins on exercise performance in non-trained rats. *Planta Medica, 64(2), 130-133.*

Wang YZ, Chen J, Chu SF, Wang YS, Wang XY, Chen NH, Zhang JT. (2009) Improvement of memory in mice and increase of hippocampal excitability in rats by ginsenoside Rg1's metabolites ginsenoside Rh1 and protopanaxatriol. *Journal of Pharmacological Sciences, 109*(4), 504–510.

Warren GL, Ingalls CP, Lowe DA, Armstrong RB. (2001). Excitation-contraction uncoupling: major role in contraction-induced muscle injury. *Exercise and Sport Sciences Reviews, 29*(2), 82-87.

Warren GL*, Lowe DA,* Armstrong RB. *(1999).* Measurement tools used in the study of eccentric contraction-induced injury. *Sports Medicine (Auckland, NZ), 27*(1)*,* 43-59.

Weber MD, Servedio FJ, Woodall WR. (1994). The effects of three modalitieson delayed onset muscle soreness. *Journal of Orthopaedic & Sports Physical Therapy, 20*(5), 236-242.

Weerakkody NS, Whitehead NP, Canny BJ, Gregory JE, Proske U. (2001). Large-fiber mechanoreceptors contribute to muscle soreness after eccentric exercise. *Journal of Pain*: *Official Journal of American Pain Society, 2*(4)*,* 209-219.

Whitehead NP, Morgan DL, Gregory JE, Proske U. (2003). Rises in whole muscle passive tension of mammalian muscle after eccentric contractions at different lengths. *Journal of Applied Physiology, 95*(3), 1224-1234.

Willems M, Hale T, Wilkinson CS. (2009). Effects of manual massage on muscle-specific soreness and single leg jump performance after downhill treadmill walking. *Sports Medicine*, *13*(2), 61-66.

Williams LO. (1957). Ginseng. *Economic Botany, 11*(4), 344-348.

Williamson A, Hoggart B. (2005). Pain: a review of three commonly used pain rating scales. *Journal of Clinical Nursing, 14*(7), 798-804.

Wills RBH, Du XW, Stuart DI. (2002). Changes in ginsenosides inAustralian-grown American ginseng plants (Panax quinquefolium L.). *Australian Journal of Experimental Agriculture, 42*(8), 1119-1123.

Winslow LC, Kroll DJ. (1998). Herbs as medicines. *Archives of Internal Medicine, 158*(20), 2192-2199.

Wood MJ, Stewart RL, Merry H, Johnstone DE, Cox JL. (2003). Use of complementary and alternative medical therapies in patients with cardiovascular disease. *American Heart Journal*, *145*(5), 806–812.

Xie HT, Wang GJ, Chen M, Jiang XL, Li H, Lv H, Huang CR, Wang R, Roberts M. (2005). Uptake and metabolism of ginsenoside Rh2 and its aglycon protopanaxadiol by Caco-2 cells. *Biological and Pharmaceutical Bulletin, 28*(2), 383-386.

Xie HT, Wang GJ, Sun JG, Tucker I, Zhao XC, Xie YY, Li H, Jiang XL,Wang R, Xu MJ, Wang W. (2005). High performance liquid chromatographic-mass spectrometric determination of ginsenoside Rg3 and its metabolites in rat plasma using solid-phase extraction for pharmacokinetic studies. *Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences,* 818(2), 167–173.

Xie JT, McHendale S, Yuan CS. (2005). Ginseng and diabetes. The *American Journal of Chinese Medicine, 33*(3), 397–404.

Xie JT, Mehendale SR, Wang A, Han AH, Wu JA, Osinski J, Yuan CS. (2004). American ginseng leaf: ginsenoside analysis and hypoglycemic activity. *Pharmacological Research: The Official Journal of the Italian Pharmacological Society, 49*(2), 113–117.

Xie JT, Shao ZH, Vanden Hoek TL, Chang WT, Li J, Mehendale S, Wang CZ, Hsu CW, Becker LB, Yin JJ, Yuan CS. (2006). Antioxidant effects of ginsenoside Re in cardiomyocytes. *European Journal of Pharmacology, 532*(3), 201–207.

Xie JT, Wang CZ, Zhang B, Mehendale SR, Li XL, Sun S, Han AH, Du W, He TC, Yuan CS. (2009). In vitro and in vivo anticancer effects of American ginseng berry: exploring representative compounds. *Biological and Pharmaceutical Bulletin*, *32*(9), 1552–1558.

Xie JT, Wu JA, Mehendale S, Aung HH, Yuan CS. (2004). Anti-hyperglycemic effect of the polysaccharides fraction from American ginseng berry extract in ob/ob mice. *Phytomedicine, 11*(2-3), 182–187.

Xie JT, Zhou YP, Dey L, Attele AS, Wu JA, Gu M, Polonsky KS, Yuan CS. (2002). Ginseng berry reduces blood glucose and body weight in db/db mice. *Phytomedicine, 9*(3), 254–258.

Xiong J, Guo J, Huang L, Meng B, Ping Q. (2008). The use of lipid-based formulations to increase the oral bioavailability of Panax notoginseng saponins following a single oral gavage to rats. *Drug Development and Industrial Pharmacy, 34*(1), 65-72.

Xiong J, Sun M, Guo J, Huang L, Wang S, Meng B, Ping Q. (2009). Enhancement by adrenaline of ginsenoside Rg1 transport in Caco-2 cells and oral absorption in rats. *Journal of Pharmacy and Pharmacology, 61*(3), 347-352.

Xu BB, Liu CQ, Gao X, Zhang WQ, Wang SW, Cao YL. (2005). Possible mechanisms of the protection of ginsenoside Re against MPTP-induced apoptosis in substantia nigra neurons of Parkinson's disease mouse model. *Journal of Asian Natural Products Research, 7*(3), 215–224.

Xu L, Chen WF, Wong MS. (2009). Ginsenoside Rg1 protects dopaminergic neurons in a rat model of Parkinson's disease through the IGF-I receptor signalling pathway. *British Journal of Pharmacology,* 158(3), 738–748.

Xu QF, Fand XL, Chen DF. (2003). Pharmacokinetics and bioavailability of ginsenoside Rb1 and Rg1 from Panax notoginseng in rats. *Journal of Ethnopharmcology, 84*(2-3), 187-192.

Xue JF, Liu ZJ, Hu JF, Chen H, Zhang JT, Chen NH. (2006). Ginsenoside Rb1 promotes neurotransmitter release by modulating phosphorylation of synapsins through a cAMP-dependent protein kinase pathway. *Brain Research, 1106*(1), 91–98.

Yagi K. (1997). Female hormones act as natural antioxidants—a survey of our research. *Acta Biochimica Polonica,44*(4), 701–709.

Ye RD, Li NL, Han JL, Kong XW, Cao R, Rao ZR, Zhao G. (2009). Neuroprotective effects of ginsenoside Rd against oxygen-glucose deprivation in cultured hippocampal neurons. *Neuroscience Research, 64*(3), 306–310.

Yeung EW, Whitehead NP, Suchyna TM, Gottlieb PA, Sachs F, Allen DG. (2005). Effects of stretch-activated channel blockers on [Ca2+]I and muscle damage in mdx mouse. *Journal of Physiology, 562*(Pt 2), 367-380.

Yokozawa T, Yasui T, Oura H. (1993). Stimulation of rna-polymerase activity by ginsenoside-Rb2 in diabetic rats. *Phytotherapy Research*, 7(3), 240–243.

Yoon SH, Han EJ, Sung JH, Chung SH. (2007). Anti-diabetic effects of compound K versus metformin versus compound K-metformin combination therapy in diabetic db/db mice. *Biological and Pharmaceutical Bulletin, 30*(11), 2196–2200.

Yoshikawa M, Murakami T, Yashiro K, Yamahara J, Matsuda H, Saijoh R, Tanaka O. (1998). Bioactive saponins and glycosides. XI. Structures of new dammarane-type triterpene oligoglycosides, quinquenosides I, II, III, IV, and V, from American ginseng, the roots of Panax quinquefolium L. *Chemical and Pharmaceutical Bulletin, 46*(4), 647–654.

Yu BP, Chung HY. (2006). Adaptive mechanisms to oxidative stress during aging. *Mechanisms of Ageing and Development, 127*(5)*, 436-443.*

Yu BP. (1994). Cellular defenses against damage from reactive oxygen species. *Physiological Reviews, 74*(1), 139–162.

Yuan CS, Dey L. (2001). Multiple effects of American ginseng in clinical medicine. *The American Journal of Chinese Medicine, 29*(3-4), 567–569.

Yuan CS, Wang CZ, Wicks SM, Qi LW. (2010). Chemical and pharmacological studies of saponins with a focus on American ginseng. *Journal of Ginseng Research, 34*(3), 160-167.

Yuan CS, Wang X, Wu JA, Attele A, Xie JT, Gu M. (2001). Effects of Panax quinquefolius L. on brainstem neuronal activities: comparison between Wisconsin- cultivated and Illinois cultivated roots. *Phytomedicine, 8*(3), 178-183.

Yuan CS, Wei G, Dey L, Karrison T, Nahlik L, Maleckar S, Kasza K, Ang-Lee M, Moss J. (2004). Brief communication: American ginseng reduces warfarin's effect in healthy patients - A randomized, controlled trial. *Annals of Internal Medicine*, 141(1), 23–27.

Yuan CS, Wu JA, Lowell T, Gu M. (1998). Gut and brain effects of American ginseng root on brainstem neuronal activities in rats. *The American Journal of Chinese Medicine, 26*(1), 47-55.

Yuan CS, Wu JA, Osinski J. (2002). Ginsenoside variability in American ginseng samples. *The American Journal of Clinical Nutrition, 75*(3), 600-601.

Yuan QL, Yang CX, Xu P, Gao XQ, Deng L, Chen P, Sun ZL, Chen QY. (2007). Neuroprotective effects of ginsenoside Rb1 on transient cerebral ischemia in rats. *Brain Research, 1167*, 1–12.

Yun TK. (2001). Brief introduction of Panax ginseng C.A. Meyer. *Journal of Korean Medical Science, 16*(Suppl.), S3-S5.

Yun TK. (2001). Panax ginseng--a non-organ-specific cancer preventive? *The Lancet Oncology, 2*(1), 49–55.

Zainuddin Z, Newton M, Sacco P, Nosaka K. (2005). Effects of massage on delayed-onset muscle soreness, swelling, and recovery of muscle function. *Journal of Athletic Training, 40*(3), 174-180.

Zhang D, Wang S, Chang Y, Han H. (1992). Effects of Panax quinquefolia saponins on hematopoietic growth factor in cyclophosphamide depressed mice. *Baiqiuen Yike Daxue Xuebao*, 18.

Zhang GZ, Liu AL, Zhou YB, San X, Jin TW, Jin Y. (2008). Panax ginseng ginsenoside-Rg(2) protects memory impairment via anti-apoptosis in a rat model with vascular dementia. *Journal of Ethnopharmacology, 115*(3), 441–448.

Zhang K, Wang X, Ding L, Li J, Qu CL, Chen LG, Jin HY, Mang HQ. (2008). Determination of seven major ginsenosides in different parts of Panax quinquefolius L. (American ginseng) with different ages. *Chemical Research in Chinese Universities, 24*(6), 707–711.

Zhao HF, Li Q, Pei XR, Zhang ZF, Yang RY, Wang JB, Li Y. (2009). Long-term ginsenoside administration prevents memory impairment in aged C57BL/6J mice by up-regulating the synaptic plasticity-related proteins in hippocampus. *Behavioural Brain Research, 201*(2), 311–317.

Zhao HF, Li Q, Zhang ZF, Pei XR, Wang JB, Li Y. (2009). Long-term ginsenoside consumption prevents memory loss in aged SAMP8 mice by decreasing oxidative stress and up-regulating the plasticity-related proteins in hippocampus. *Brain Research, 1256*, 111–122.

Zhao WJ, Li PY. (2004). Ginsenoside Re improved memory impairment in aged rats and mice. *Neurobiology of Aging, 25*(2 Suppl.), S582–S583.

Zheng BC. (1985). Shennong's herbal- One of the world's earliest pharmacopoeia. *Journal of Traditional Chinese Medicine, 5*(3), 236.

Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen CJ. (2004). Molecular mechanisms and clinical applications of ginseng root for cardiovascular disease. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 10*(8), RA187–192.

Zhuang M, Wu Y, Li M, Shu Y. (1996). Effects of some medicinal polysaccharides on immune deficiency in animal models induced by cobra anticomplementary factor. *Journal of Natural Toxins, 5*(2), 161–164.

# 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**

http://www.csep.ca/cmfiles/publications/parq/par-q.pdf

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

# PAR-Q & YOU

**(A Questionnaire for People Aged 15 to 69)**

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

| YES | NO | | |
|---|---|---|---|
| ☐ | ☐ | 1. | **Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?** |
| ☐ | ☐ | 2. | **Do you feel pain in your chest when you do physical activity?** |
| ☐ | ☐ | 3. | **In the past month, have you had chest pain when you were not doing physical activity?** |
| ☐ | ☐ | 4. | **Do you lose your balance because of dizziness or do you ever lose consciousness?** |
| ☐ | ☐ | 5. | **Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?** |
| ☐ | ☐ | 6. | **Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?** |
| ☐ | ☐ | 7. | **Do you know of any other reason why you should not do physical activity?** |

**If you answered**

## YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

## NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

**DELAY BECOMING MUCH MORE ACTIVE:**

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

**No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.**

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

**Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.**

CSEP | SCPE

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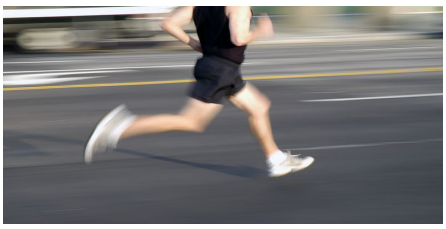
# Appendix C

## 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 medal 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)

| Subject # | Fat (g) | Protein (g) | Carbohydrate (g) | Energy (kcal) |
|---|---|---|---|---|
| 1 | 109 | 110 | 244 | 2402 |
| 2 | 119 | 193 | 366 | 3314 |
| 3 | 120 | 137 | 318 | 2877 |
| 4 | 72 | 102 | 326 | 2340 |
| 5 | 93 | 82 | 321 | 2470 |
| 6 | 29 | 76 | 273 | 1675 |
| 7 | 48 | 131 | 228 | 1793 |
| 8 | 80 | 292 | 217 | 2721 |
| 9 | N/A | | | |
| 10 | 169 | 223 | 402 | 4090 |

# Appendix E

Certificate of Approval of Human Ethics

Western Research

Research 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:**

| Document Name | Comments | Version Date |
|---|---|---|
| Western University Protocol | (including instruments noted in section 8.1) | |
| Letter of Information & Consent | | |
| Advertisement | | |

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/ICH 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 IRB registration number IRB 00000940.

**Ethics Officer to Contact for Further Information**

| | | |
|---|---|---|
| Janice Sutherland (jsutherl@uwo.ca) | Grace Kelly (grace.kelly@uwo.ca) | Shantel Walcott (swalcot@uwo.ca) |

*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. 519.850.2466 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