EFFECTS OF SHORT-TERM MONTMORENCY POWDERED TART CHERRY SUPPLEMENTATION ON MUSCLE DAMAGE, SORENESS PERCEPTION, INFLAMMATION, OXIDATIVE STRESS, AND PERFORMANCE SURROUNDING ACUTE BOUTS OF INTENSE ENDURANCE AND STRENGTH EXERCISE

A Dissertation

by

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ABSTRACT

The purpose of this research was to examine whether short-term ingestion of a powdered tart cherry supplement surrounding intense resistance and endurance exercise attenuates muscle soreness, while reducing markers of muscle damage, inflammation, and oxidative stress.

23 healthy, resistance-trained men (20.9±2.6 yr, 14.2±5.4% body fat, 63.9±8.6 kg FFM) were recruited for the resistance study, while 27 endurance trained runners or triathlete (21.8±3.9 yr, 15.0±6.0% body fat, 67.4±11.8 kg) men and women were examined in the endurance study. Subjects were matched based on relative maximal back squat strength or average projected race pace, age, body weight, and fat free mass. Subjects were randomly assigned to ingest, in a double blind manner, capsules containing a placebo (P) or powdered tart cherries [CherryPURE®] (TC). Participants supplemented one time daily (480 mg/d) for 10-d including the day of exercise up to 48-hr post-exercise. Resistance study subjects performed 10 sets of 10 repetitions at 70% 1-RM back squat exercise, while endurance subjects completed a half-marathon run (21.1 km) under 2-hr (111.98±11.9 min). Fasting blood samples and quadriceps muscle soreness ratings were taken pre-exercise, 60-min, 24-h, and 48-h post-exercise and analyzed by MANOVA with repeated measures.

Muscle soreness perception in the vastus medialis (¼) (p=0.10) and the vastus lateralis (¼) (p=0.024) tended to be lower in TC over time compared to P following resistance exercise. TC induced changes in serum creatinine (p=0.03, p=0.047) and total

protein ($p=0.018$, $p=0.081$) that were lower over time and smaller from pre-lift levels compared to P in trained individuals. Despite lower TAS activity pre-run in TC compared to P (endurance), changes from pre-run levels revealed a linear increase in TAS activity during recovery in TC that was statistically different from P and pre-run levels. IL-6 levels (endurance) were lower in TC compared to P over time ($p=0.053$). Subjects in the TC group tended to have smaller deviations from predicted race pace ($p=0.091$) compared to P (endurance). Short-term supplementation of Montmorency powdered tart cherries surrounding a single bout of intense exercise, appears to be an effective dietary supplement to attenuate muscle soreness and markers of muscle catabolism, while reducing inflammatory stress, better maintaining redox balance, and increasing performance in trained individuals.

DEDICATION

To my parents, Susan and Kenneth Levers; to my grandparents, Helen and Clarence Levers, and Phyllis and Burton Krotosky; to my great aunt, Aunt Irma Haig; and to my loving girlfriend, Madeline Corwin.

No matter the endeavor, you have always been there for me with the utmost love and support that has given me the drive to accomplish great things no matter the obstacle. Each of you, in your own way and through your own life challenges, have instilled the value of hard work, steadfast determination, unwavering commitment to excellence, strength of character, and an unselfish care for others in the pursuit of success across all endeavors. Through your collective example, love, and belief in my success, I have become the man that I am today. Every day, I am reminded of the strength and courage that each of you have instilled in me as I strive to pay it forward and make a difference in the lives of others. Without you, none of this would have been possible and for that, I am forever grateful.

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NOMENCLATURE

ESNL	Exercise and Sport Nutrition Laboratory
TCE	Tart Cherry Endurance Study
TCR	Tart Cherry Resistance Study
FAM	Familiarization Session
BASE	Baseline Testing Session (Pre-Supplementation)
T1-PRE	Testing Session #1: Pre-Exercise (Supplementation Day 8)
T1-POST	Testing Session #1: 60-min Post-Exercise
T2	Testing Session #2: 24-h Post-Exercise (Supplementation Day 9)
T3	Testing Session #3: 48-h Post-Exercise (Supplementation Day 10)
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
HR	Heart Rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
DEXA	Dual X-ray Absorptiometry
BMD	Bone Mineral Density
LM	Lean Mass
FFM	Fat Free Mass
FM	Fat Mass
GPRS	Graphic Pain Rating Scale
VAS	Visual Analog Scale

PPT	Pain Pressure Threshold
DOMS	Delayed Onset Muscle Soreness
Algo I	Algometer Location #1: Vastus Medalis ¼
Algo II	Algometer Location #2: Vastus Lateralis ¼
Algo III	Algometer Location #3: Vastus Lateralis ½
VM	Vastus Medalis
VL	Vastus Lateralis
LIST	Loughborough Intermittent Shuttle Test
IK	Isokinetic
MVC	Maximal Voluntary Contraction
MVIC	Maximal Voluntary Isometric Contraction
1-RM	1-Repetition Maximum
Reps	Repetitions
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CPK	Creatine Phosphokinase
UA	Uric Acid
LDH	Lactate Dehydrogenase
Test/Cort	Testosterone/Cortisol Ratio
NT	Nitrotrosine

SOD	Superoxide Dismutase
TAS	Total Antioxidant Status
TAC	Total Antioxidant Capacity
PAC	Plasma Antioxidant Capacity
ORAC	Oxygen Radical Absorbance Capacity
FRAP	Ferric Reducing Ability of Plasma
TBARS	Thiobarbituric Acid Reactive Substances
LOOH	Lipid Hydroperoxides
PC	Protein Carbonyls
MDA	Malondialdehyde
GPx	Glutathione Peroxidase
GSSH/TGSH Ratio	Glutathione Ratio (Oxidized Glutathione/Total Glutathione)
TNF-α	Tumor Necrosis Factor Alpha
IFN-γ	Interferon Gamma
IL	Interleukin
MPO	Myeloperoxidase
CRP	C-Reactive Protein
hsCRP	High Sensitivity C-Reactive Protein
SAA	Serum Amyloid A
NO	Nitric Oxide
RANTES	Regulated on Activation, Normal T Expressed and Secreted
WBC	White Blood Cell

LYMPH	Lymphocyte
MID	Mid-Range Absolute Count
MCP-1	Monocyte Chemotactic Protein 1
MIP-1β	Macrophage Inflammatory Protein 1β
GRAN	Granulocyte Absolute Count
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
RBC	Red Blood Cell
PLT	Platelet
MVP	Mean Platelet Volume
HGB	Hemoglobin
RDW	Red Cell Distribution Width
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
VLDL	Very Low Density Lipoprotein

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CHAPTER I

INTRODUCTION AND RATIONALE*

Background

Acute bouts of strenuous aerobic performance facilitate an exercise-induced stress response characterized by mechanical muscle damage, oxidative damage, and inflammation that parallels the physiological stress response associated with many adverse traumatic cardiovascular events and illnesses (27, 54, 113, 129, 192, 195). A single large volume, high intensity strength training workout also activates a repetitive load-induced stress response characterized by structural muscle damage, oxidative stress, and inflammation that facilitates the release of intramuscular proteins in the systemic circulation that typically is associated with cardiovascular dysfunction, invasive surgery, and disease (20, 27, 54, 86, 113, 129, 192, 195). The repetitive nature of eccentric muscular contractions during bouts of high intensity exercise will cause muscular injury as a result of ultrastructural disruptions (60, 106, 163, 192) that ultimately leads to a muscular repair sequence of degeneration, inflammation, regeneration, and fibrosis (185, 192). Muscle soreness following exercise is not the direct result of inflammation, but rather a product of high nociceptor and mechanoreceptor sensitivity to the potent chemicals and by-products released during muscular degeneration. As a result, higher volumes of repetitive muscular stress and/or large metabolic demands from the oxidative energy systems (12) significantly increases free radical production beyond the capacity

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*Portions reprinted from "Effects of powdered Montmorency tart cherry supplementation on an acute bout of intense lower body strength exercise in resistance trained males" by Levers K, Dalton R, Galvan, E, et al. 2015. *Journal of the International Society of Sport Nutrition*, 12, 1-23, Copyright 2015 by Kyle Levers.

of the endogenous antioxidant systems. This muscle damaging exercise and subsequent free radical production ultimately facilitates excessive cell damage, altered cell signaling (9, 147, 148), decreased cellular performance (9, 114, 147, 148), lipid peroxidation, oxidation of proteins and glutathione, and subsequent DNA damage (113, 124).

Millions of people, including athletes, around the world (163, 192) use non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen to help reduce pain and inflammation. NSAID use mitigates the inflammatory response via non-specific inhibition of the cyclooxygenase (COX -1 and COX-2) enzymes that regulate the production of inflammatory-stimulating prostaglandins (12, 163, 192). The effectiveness of NSAIDs to relieve inflammation and perceptions of muscle soreness remains highly controversial due to conflicting reports when administration follows bouts of exercise (18, 51, 137, 145, 163, 186, 187, 192), despite popular utilization among athletes and the general active population. To further complicate the NSAID use debate, researchers have demonstrated that muscle protein synthesis and the function of satellite cells in skeletal muscle hypertrophy are compromised when COX enzymes are inhibited (17, 122, 135, 159, 187), while other investigators have found no NSAID effect on the post-exercise anabolic processes within muscle (24, 123, 141).

Effective and efficient recovery from exercise, including attenuation of pain and inflammation as a result of training stress and injury, is paramount to all athletes, particularly athletes during micro- or mesocycles of high training and/or competition volume that require an expedited return to peak performance (9, 13). Antioxidant supplementation surrounding bouts of aerobic exercise has gained significant traction

over the last 20 years (191), particularly with the uncertainty of NSAID effects, due to the success of these supplements and functional foods in the clinical population (7, 91, 92, 139, 150, 207). The use of antioxidant supplementation in athletic applications to help fortify the body's endogenous antioxidant response while attenuating muscle damage and inflammation has spurred some success with supplements such as ascorbic acid (vitamin C) (6, 22, 57, 95, 120, 184) and α-tocopherol (vitamin E) (12, 57, 117, 120, 142, 160). Supplementation with vitamins C and E (independently or in combination with N-acetylcysteine, β-carotene, or α-lipoic acid) to improve exercise performance has also been met with controversy due to conflicting reports of effectiveness (8, 23, 67, 113, 157, 165, 181, 182, 205) and even risks of pro-oxidant effects that target muscle protein anabolism, (32, 37, 156, 179), endogenous antioxidant capacity (156), and mitochondrial biogenesis (176) in the post-exercise recovery period. However, some studies have demonstrated neither detriment nor benefit of these antioxidants to muscle recovery and endurance training adaptations (157, 205).

Due to the debate surrounding the use of NSAIDs and individual antioxidant components (e.g. ascorbic acid and α-tocopherol) to reduce pain and inflammation in disease, health, and exercise applications, nutritional research has more recently shifted a focus toward the study of phytochemical-containing fruits and other functional foods that seem to provide a beneficial anti-inflammatory and antioxidant effect (11, 40). Particular phenolic compounds, such as flavonoids and anthocyanins, may act synergistically with other compounds contained within the fruit or food to provide an overall exercise recovery benefit that may not be derived from vitamin or synthetic

sources (9, 12). A wide variety of antioxidant and polyphenol-containing functional foods such as purple sweet potatoes (33, 177, 180), beet root juice (203, 204, 210), green tea (87, 136), cranberries, grape extract (102), chokeberries (144), pomegranate juice and ellagitannin extract (189, 190), spinach (16), and blueberries (114) have verified performance enhancing and exercise recovery benefits. Tart (e.g. Mortmorency) and sweet cherries (e.g. Bing) have received substantial attention within the clinical literature and the nutritional supplement industry due to their high anthocyanin content (29, 30, 197) that has demonstrated consistent benefit as a naturally occurring intervention to aid improvement in health (82, 93, 119, 188), inflammatory-related disease states (e.g. cardiovascular disease, diabetes, osteoarthritis, gout) (15, 82, 93, 119, 164), and sleep quality (75, 143). The increased clinical nutrition success of both tart cherry concentrate and cultivar-blended juice supplementation spurred the potential for exercise-based research and application to help increase performance by theoretically reducing muscle damage, oxidative stress, and inflammation (9). The incorporation of a naturally occurring food component with phytochemicals (e.g. cherries) that has known antioxidant and anti-inflammatory properties (82, 93, 119, 126, 166, 188, 198, 199) into a post-exercise meal or supplement, such as a carbohydrate-protein mixture (38, 39, 77, 162) known attenuate the muscle damaging and catabolic effects of prolonged endurance exercise, may prove to be highly beneficial in future acute situations of performance recovery.

Specific Aim

Is supplementation with a powdered tart cherry supplement derived from tart cherry skins more efficacious than a placebo as well as previously studied tart cherry juices, blends, and concentrates in improving performance while reducing markers of oxidative stress, inflammation, muscle damage, muscle soreness, and strength losses during recovery?

Purpose of the Research

The primary objective of this research is to ascertain if this novel tart cherry supplement would facilitate similar attenuation of oxidative stress, inflammation, muscle damage, and muscle soreness as the tart cherry cultivar-blended juices and juice concentrates supplemented in the previous tart cherry supplementation-based studies in the literature. The secondary objective of this study was to determine whether short-term (10-d) supplementation with a powdered form of tart cherry skins prior to and following a single resistance or endurance exercise challenge will effectively reduce markers of oxidative stress, inflammation, muscle damage, muscle soreness, and/or attenuate resistance-exercise based strength losses during recovery.

General Research Overview

This will be a series of two double-blind 10-d supplementation studies that will compare the effects of CherryPURE™ (powdered tart cherry supplement) and a placebo on markers of oxidative stress, inflammation, muscle damage, muscle soreness, and strength changes during subsequent exercise performance surrounding acute bouts of intense endurance or resistance exercise. Subjects will be randomly assigned to one of

two groups in each of the studies in paired-match control format: 1) CherryPURE™ or 2) Placebo. Both groups will return to the lab for a total of four testing sessions following the initial familiarization: baseline (approximately 1-wk pre-supplement), Day 8 (T1-exercise and 60-m post-exercise), Day 9 (24-h post-exercise), and Day 10 (48-h post-exercise). Within the endurance study, anthropometrics, whole blood and serum markers of general clinical health, lipid profiles, measures of muscle soreness, markers of muscle damage, oxidative stress, inflammation, and immune cell counts will be recorded at each testing session, while measurement of body composition will only occur at baseline for purposes of subject stratification. The resistance study will follow a similar structure with anthropometrics, isokinetic leg extension maximal voluntary contraction (MVC) performance on the dominant leg, whole blood and serum markers of general clinical health, lipid profiles, measures of muscle soreness, markers of muscle damage, oxidative stress, inflammation, and immune cell counts will be recorded at each testing session, while measurement of body composition and barbell back squat 1-repetition maximum (1-RM) will only occur at baseline for purposes of subject stratification.

Hypotheses

Tart Cherry Resistance Central Hypotheses

H_o1: Isokinetic flexion, extension, and total work performed during the 48-h post-lift recovery will be greater with tart cherry supplementation.

H_o2: There will be no significant difference between groups in pre-lift isokinetic flexion, extension, and total work performed.

H_o3: Vastus medalis (¼) muscle soreness perceptions over the 48-h post-lift recovery will be lower with tart cherry supplementation.

H_o4: Vastus lateralis (¼) muscle soreness perceptions over the 48-h post-lift recovery will be lower with tart cherry supplementation.

H_o5: Vastus lateralis (½) muscle soreness perceptions 60-min post-lift will be lower with tart cherry supplementation.

H_o6: There will be no significant differences between groups in vastus lateralis (½) muscle soreness pre-lift, 24-h, and 48-h post-lift.

H_o7: There will be no significant difference between groups in pre-lift perceptions of quadriceps muscle soreness.

H_o8: Serum markers of muscle catabolism, secondary muscle damage, and physiological/renal stress over the 48-hr post-lift recovery will be lower with tart cherry supplementation.

H_o9: There will be no significant differences between groups in pre-lift serum markers of muscle catabolism, secondary muscle damage, and physiological/renal stress.

H_o10: Serum cortisol levels (marker of physiological stress and the catabolic state) 60-min post-lift will be lower with tart cherry supplementation.

H_o11: There will be no significant differences between groups in serum cortisol levels pre-lift, 24-h, and 48-h post-lift.

H_o12: There will be no significant differences between groups in serum testosterone levels and the testosterone/cortisol ratio (measure of anabolic/catabolic activity) pre-lift or over the 48-h post-lift recovery.

H_o13: There will no significant differences between groups in serum markers of free radical production, oxidative stress, or antioxidant/anti-radical activity pre-lift or over the 48-h post-lift recovery.

H_o14: There will be no significant differences between groups in serum pro-inflammatory cytokines and chemokines pre-lift or over the 48-h post-lift recovery.

H_o15: There will be no significant differences between groups in serum anti-inflammatory cytokines pre-lift or over the 48-h post-lift recovery.

H_o16: There will be no significant differences between groups in whole blood immune cell counts pre-lift or over the 48-h post-lift recovery.

Tart Cherry Endurance Central Hypotheses

H_o17: There will be no significant differences between groups in half-marathon projected and actual finish times.

H_o18: Vastus medalis (¼) muscle soreness perceptions over the 48-hr post-run recovery will be lower with tart cherry supplementation.

H_o19: Vastus lateralis (¼) muscle soreness perceptions over the 48-hr post-run recovery will be lower with tart cherry supplementation.

H_o20: Vastus lateralis (½) muscle soreness perception over the 48-hr post-run recovery will be lower with tart cherry supplementation.

H_o21: There will be no significant difference between groups in pre-run perceptions of quadriceps muscle soreness.

H_o22: Serum markers of muscle catabolism, secondary muscle damage, and physiological/renal stress will be lower over the 48-hr post-run recovery with tart cherry supplementation.

H_o23: There will be no significant group differences between groups in pre-run markers of muscle catabolism, secondary muscle damage, and physiological/renal stress.

H_o24: Serum cortisol levels and the testosterone/cortisol ratio 60-min post-run will be lower with tart cherry supplementation.

H_o25: There will be no significant differences between groups in pre-run, 24-h, and 48-h post-run serum cortisol levels and the testosterone/cortisol ratio.

H_o26: There will be no significant differences between groups in serum testosterone levels pre-run or over the 48-h post-run recovery.

H_o27: Serum markers of free radical production and oxidative stress over the 48-hr post-run recovery will be lower with tart cherry supplementation.

H_o28: Serum markers of antioxidant/anti-radical activity over the 48-hr post-run recovery will be higher with tart cherry supplementation.

H_o29: There will be no significant difference between groups in pre-run serum markers of free radical production, oxidative stress, and antioxidant/anti-radical activity.

H_o30: Serum pro-inflammatory cytokines and chemokines over the 48-hr post-run recovery will be lower with tart cherry supplementation.

H_o31: There will be no significant difference between groups in pre-run serum pro-inflammatory cytokines/chemokines anti-inflammatory cytokines.

H_o32: Serum anti-inflammatory cytokines over the 48-hr post-run recovery will be lower with tart cherry supplementation.

H_o33: There will no significant differences between groups in whole blood immune cell counts pre-run or over the 48-h post-run recovery.

Delimitations

Tart Cherry Resistance & Endurance Delimitations

1. Subjects refrained from the consumption of NSAIDs and all exercise 48-h prior to each testing session (familiarization, baseline, days 8-10).
2. Subjects completed a 4-d dietary record during the first 7-d of the supplementation period and were advised to maintain a consistent diet over the study duration.
3. Subjects were advised to maintain their normal workout/training regimen over the study duration (on permitted days).
4. Subjects fasted for at least 10-h prior to each testing session.
5. Subjects were instructed to consume all supplements according to directions provided, specifically ingesting one supplement capsule per day in the morning at 0800 in conjunction with the breakfast meal.

6. Subjects had their body composition measured using dual x-ray absorptiometry (DEXA).
7. Blood samples were obtained from subjects at the familiarization (pre-supplementation), pre-exercise, 60-min, 24-h, and 48-h post-exercise.
8. Perception of soreness measurements were determined using 50 N of force applied with an algometer and perceptions recorded on a graphic pain rating scale.
9. Perceptions of muscle soreness were analyzed on the quadriceps muscle group at three distinct locations between the superior border of the patella and greater trochanter: ¼ of the distance on the vastus medalis, ¼ of the distance on the vastus lateralis, and ½ of the distance on the vastus lateralis.
10. Perceptions of muscle soreness were analyzed pre-exercise, 60-min, 24-h, and 48-h post-exercise.
11. Subjects refrained from the consumption of all food and beverages, except water, between pre-exercise testing and the exercise performance challenge.
12. Subjects performed to their maximal ability on all exercise and testing measures.

Tart Cherry Resistance Delimitations

13. This study included resistance trained males ages 18-40 with barbell back squat experience.
14. The recruited subjects were required to squat at least 1.5 times their body weight.
15. Subjects were paired based on relative barbell back squat strength, fat free mass, body weight, and age.

16. The exercise performance challenge was 10 sets of 10 repetitions at 70% of the subject's 1-RM.
17. Maximal voluntary contractions (MVC) were determined during isokinetic knee extension and flexion on the dominant leg at 60°/sec.
18. Subjects self-reported their dominant leg to be tested during isokinetic maximal voluntary contractions.
19. Isokinetic MVC performance was tested at the FAM session (pre-supplementation), pre-lift, 60-min, 24-h, and 48-h post-lift.

Tart Cherry Endurance Delimitations

20. This study included endurance trained males and females ages 18-40 with competitive runner experience.
21. The recruited subjects were required to run a half-marathon (21.1 km) in less than 2-h.
22. Subjects were required to accurately report previous running performance.
23. Subjects were paired based on previous performance running pace/predicted finish time, fat free mass, body weight, and age.
24. The half-marathon race started at 0800 and be run on a pre-planned, closed road course on the campus of Texas A&M University. The race will require subjects to run 2 laps around a 10.54 km road course.
25. Subjects were provided water and glucose-electrolyte sports drinks at hydration stations located at 4 points along the planned route ad libitum.
26. Subjects were allotted a 20-min warm-up period prior to the half-marathon.

27. Subjects were not allotted a running or active cool down following the half-marathon. Only minimal ambulation was allowed up to the 60-min post-run testing session.
28. There were not any performance tests as part of the study protocol.

Limitations

1. The subjects were individuals from the Texas A&M University community and surrounding fitness facilities that respond to recruitment fliers and emails; therefore the selection process will not truly random.
2. While there may be some variations in testing times and dietary intake, all efforts were made to conduct testing sessions at the same approximate time to account for diurnal variations. Subjects were instructed to maintain a consistent diet throughout the duration of the study.
3. Subject intrinsic motivations and effort during the exercise bout and subsequent performance testing may not have been maximized at each testing session.
4. Subjects may not have followed the supplement instructions as defined during the familiarization session or during supplement distribution.
5. All subjects were instructed to maintain their normal training program on permitted days as defined by the study protocol. However, exercise habits during the duration of the study may have changed and therefore changes in performance measures may have been influenced by individual differences in training rather than the assigned supplement.

6. All equipment was calibrated according to manufacturer guidelines and all samples were run in duplicate to reduce likelihood of error. However, there may have still been some innate limitations of the laboratory equipment that was used for data collection and analysis.
7. All blood samples were handled and processed uniformly across participants and testing sessions. However, due large subject volume in a limited amount of time (TCE) and multiple laboratory staff working with study subjects there was a possibility that sample handling may be completely consistent.
8. Subjects were recruited into each study by set minimum study inclusion/exclusion criteria and matched based on specific study measures. However, there still might have been innate imitations and variability in matching subjects based on a limited set of study measures compared to a cross over study design.

Assumptions

1. Subjects followed the overall protocol that was explained to them during the familiarization session.
2. Subjects adhered to the 10-d supplementation protocol explained to them during the familiarization session.
3. Subjects refrained from NSAID utilization and any type of physical activity 48-h prior to each of the 5 testing sessions (familiarization, baseline, days 8-10).
4. Subjects answered the entrance questionnaires accurately and honestly prior to being accepted into the study.

5. Subjects honestly answered, to the best of their ability, the graphic pain rating scale (GPRS) in response to algometer quadriceps muscle soreness measurement within each of the 4 testing sessions.
6. All laboratory equipment was calibrated and functioning properly prior to all testing sessions.
7. The population, which the sample was drawn from, was normally distributed.
8. The variance among the population sample was approximately equal.
9. The sample was randomly assigned to the different supplement groups. Subjects and researchers remained blinded to their assigned supplement throughout the study.
10. Subjects maintained a consistent dietary intake and exercise regimen (when permitted) throughout the duration of their respective studies.
11. Subjects performed at their maximal potential within the primary exercise bout and in subsequent performance testing (if required).
12. Subjects who are dropped from study participation, particularly after starting supplementation, were honest in their reasoning after their initial commitment following the familiarization session and informed consent signing.
13. Subjects honestly recorded their 4-d dietary intake during the first 7-d of supplementation.
14. Subjects fasted for 10-h prior to each testing session that involved a fasting blood draw (familiarization, baseline, days 8-10) and maintained a consistent hydration status across all testing sessions within the study protocol.

15. Tart cherry endurance subjects accurately and correctly reported past endurance performance results in the initial study paperwork.

CHAPTER II

REVIEW OF LITERATURE

Introduction

The primary goals of athletic competitors all stem from a common and continued desire to improve performance through optimization of training and recovery. As a result of extensive training regimens and physiological demands of long duration, repetitive endurance exercise or highly intense resistance training bouts, the body progresses through a condition referred to as exercise-induced muscle damage. The muscular damage, breakdown, and resulting inflammatory response as a result of demanding or unfamiliar exercise are typically associated with impaired muscle function and delayed onset muscle soreness (DOMS). In training program design and implementation of periodization schemes, coaching professionals attempt to plan exercise sessions to account for this physiological response to training stress. However, trained individuals likely have naturally adapted to handle increasing exercise demands as a result of a repetitive training load if the regimen remains consistent. Unfamiliar exercise or additions to training programs typically cause greater exercise-induced muscle damage as a result of increased intramuscular stress, damage, and catabolism. Reducing muscle soreness, pain, and inflammation to help expedite the recovery of muscle function, athletes will traditionally resort to ingesting supplement remedies.

Contributing Models of Delayed Onset Muscle Soreness

Delayed onset muscle soreness (DOMS) is clinically classified as a type I muscle strain that presents with tenderness and stiffness in the muscle belly with sensitivity

specifically associated with movement and/or palpation (31, 68). Typically, the muscle tenderness and sensitivity is initially focused in the distal aspect of the muscle due to the high concentration of nocioreceptors in the myotendinous junction and will dissipate progressively over the 48-h post-damaging exercise period (31, 111). Despite the prevalence of DOMS among recreationally trained individuals and athletes, there is not any one theory that has been identified to describe the primary mechanism of DOMS development following muscle damaging exercise. Due to the fact that one model cannot explain all aspects of the DOMS phenomenon, researchers have proposed an integration of several models (4, 31, 171).

As part of the connective tissue and muscle damage theories, any type of eccentric muscle action or braking force produces higher tensile forces than those that may even be experienced during concentric muscle action (31, 36, 68). The high muscular tension places great strain on connective tissue located at the myoteninous junction and immediately surrounding distal muscle fibers (31, 173). As a result of this great muscular tension produced, the sarcolemma is significantly damaged, causing a large calcium accumulation. This accumulation effects ATP production and calcium balance within the muscular environment that activates enzymes to breakdown the excessive calcium (31, 68). Unfortunately, the activation of these enzymes causes major degradation of the sarcomere z-line and contractile proteins troponin and tropomyosin (4, 31, 68). Further damage to the sarcolemma due to calcium accumulation can also be caused by activation of proteases and phospholipases responsible for the production of leukotrienes and prostaglandins (4, 5, 31).

As a result of the tissue damage, there is a large increase in circulating neutrophils to drive the immune response. Due to the sarcomere damage and subsequent increases in muscle cell membrane permeability, intramuscular cellular components leak in to the surrounding sarcoplasm and plasma serving as common markers of muscle and tissue damage (e.g. CK, myoglobin, creatinine, hydroxproline) (21, 31, 128). The circulating neutrophils over the hours post-exercise induced muscular injury are attracted to the site of damage through the progressive leakage of cellular components and histamines into the local plasma (31, 72). The arrival of neutrophils at the site of muscular injury serves to call monocytes (eventually macrophages) to the area, peaking in concentration at 48-h post-exercise (31, 68). As a result of the increase inflammatory environment, macrophages produce also prostaglandins (PGE_2) to help sensitize the local nerve endings to changes in mechanical, chemical, or thermal stimulation (31). The breakdown of cellular components and phagocytosis as the repair process is initiated causes an accumulation of histamine, potassium, and kinins along with elevated fluid pressure and temperature within the muscular environment (31, 59, 68). The previous activation and sensitization of nocioreceptors signals soreness and pain within the muscular area of damage (31). While the composition of this proposed multiple theory model needs to be investigated through future research, this provides a sound basis for the examination of the theorized mechanisms of supplementation to aid in helping to attenuate effects of contributing mechanisms to muscle soreness and pain as well as primary and secondary muscle damage.

Oxidative Stress and Inflammatory Pathway Interrelationship

At the cellular level, oxidative stress occurs due to an imbalance that occurs between oxidant production and the capacity of the cell to balance oxidant production through antioxidant mechanisms (146). The cellular environment has a strategically constructed labyrinth of enzymatic and non-enzymatic antioxidants that exist both inside and outside of the cellular environment to effectively remove reactive oxygen species (ROS) and reactive nitrogen species (RNS) to optimize redox balance (146). More specifically, cells employ multiple strategies utilizing endogenous and exogenous antioxidants to help safely and effectively neutralize ROS/RNS production. Antioxidants have the ability to scavenge for ROS/RNS and convert potent ROS/RNS into less active forms to help reduce cellular damage potential and also act to prevent low potency ROS/RNS conversion to more damaging oxidant species forms (146). When ROS/RNS production overwhelms cellular antioxidant mechanisms to the point where oxidants outnumber the available antioxidants, oxidative stress occurs.

Over the course of strenuous exercise bouts, contracting skeletal muscle produces free-radicals, ROS, and RNS from a multitude of cellular sources within the musculature (79, 146, 153). Within the current literature, evidence points to mitochondrial radical production as the primary source within skeletal muscle during an exercise bout. The mitochondria has been charged with producing skeletal muscle radicals as an ill-intended derivative of oxidative metabolism, namely generating xanthine oxidase, NADPH oxidase, and nitric oxide through nitric oxide synthase (79, 146, 153-155). In addition to the mitochondria (complexes I and III of the electron transport chain), sarcoplasmic

reticulum, transverse tubules, sarcolemma, and the sarcoplasm/cytosol are also greatly responsible for ROS/RNS production (103, 149). More specifically, production of superoxide within the triad of calcium release (e.g. sarcolemma, transverse tubules, and sarcoplasmic reticulum) is derived from NADPH oxidases (148) in addition to the potential for superoxide production from the sarcolemma due to phospholipase-A_2 dependent mechanisms (81, 103). Intensive exercise bouts or repetitive eccentrically-based muscle actions causing excessive muscle damage and eliciting an inflammatory response creates a secondary source of free-radical production within the muscle cell environment. The aforementioned activation of phagocytosis and neutrophil respiratory bursts produce significant ROS that have been involved in creation of secondary muscle damage following the primary muscular mechanical disruption (77, 104). Other secondary sources of ROS production within the muscular environment include autoxidation of catecholamines and radical formation from the breakdown of iron-containing proteins (79, 148).

Due to the multitude of free-radical and oxidant sources and significant increase in production within the muscular environment as a result of intense physical exercise, endogenous antioxidant capacities must be able to adapt to the increased demand to prevent oxidative damage to proteins, lipids, and DNA (146). More specifically, in response to exercise-induced skeletal muscle contraction, the muscle environment contains multiple endogenous antioxidant enzymes that balance ROS concentrations including CuZn-superoxide dismutase (sarcoplasm), Mn-superoxide dismutase (mitochondria), catalase, and glutathione peroxidase (sarcoplasm and mitochondria) (55,

103). Some of the lipid soluble components found within the sarcolemma (vitamin E and carotenes) and water soluble antioxidants located throughout the muscle cell (vitamin C and glutathione) are also found as primary bioactive constituents in tart cherries that may help to aid in the antioxidant defense during times of high oxidative stress (e.g. high-intensity or long duration exercise) or during low antioxidant concentrations (55, 103). Glutathione as a water soluble component is the most effective and ubiquitous antioxidant within the muscle cell as usually monitored for an indication of redox balance within the cell via the ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) (55, 103).

The exercise-induced production of ROS within contracting skeletal muscle provides an important link to inflammation through cytoplasm-nuclear communication and subsequent influences of gene expression. The production of ROS within skeletal muscle has been proven to affect multiple signaling pathways, with the most notable being those pathways that govern the inflammatory and proteolytic/catabolic response. Responsible for inflammation among other cellular responses, cell signaling molecule NF-κB is activated as a free dimer to travel across the nuclear membrane through phosphorylation of its inhibitor molecule (IκB) by IκB kinase (IKK) and impact gene expression within the muscular nucleus leading to an increased inflammatory response (inflammatory mediators: cytokines, enzymes, chemokines, and adhesion molecules) [21,22,26]. During periods of high-intensity exercise, where endogenous antioxidant production may not be sufficient to deal with the elevated production of ROS, dietary consumption of an antioxidant supplement may help to attenuate the effect of ROS on

muscular cellular signaling pathways that affect the inflammatory response through alterations in gene expression.

In addition to the production of ROS and RNS during exercise-induced skeletal muscle contraction that leads to a pro-inflammatory response, the synthesis of arachidonic acid and subsequent metabolites also significantly contribute to increases in post-exercise inflammation. Arachidonic acid is a second messenger molecule released by phospholipase A_2 (PLA_2) at which point it is metabolized by cyclooxygenase I and II (COX I and COX 2) and lipoxygenase (LOX) pathways in various eicosanoids that produce prostaglandins and leukotrienes (66). The COX enzymes are important in inflammatory processes as they are expressed in various organs (COX-1), microphages, and mast cells (COX-2) in addition to roles in angiogenesis, cell death/proliferation, and carcinogenesis (66, 126). Cyclooxygenases are stimulated to release prostaglandins that typically act as pro-inflammatory mediators (e.g. PGE_2). Lipoxygenases (typically 5-LOX generated within neutrophils) in the metabolism of arachidonic acid produce hydroxy acids and leukotrienes that are charged as potent chemoattractant mediators of the inflammatory response (66).

Cyclooxygenase enzyme or pathway inhibition can typically be accomplished by over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) as detailed in the next section, however, due to the inability to control the potential side-effects of these drugs, various anthocyanin, flavonoid, and polyphenol containing foods, juices, and nutritional supplements have been recommended instead due to their comparable effectiveness to the over-the-counter drugs. Several of the bioactive phytochemicals contained within

functional foods (anthocyanins, flavonoids, and polyphenols) will be discussed in later sections to define their ability to inhibit enzymes and production of metabolites all along the arachidonic acid metabolic pathway to help reduce the subsequent pro-inflammatory stimulus following a bout of exercise.

However, some NSAID and antioxidant research described in the upcoming sections have demonstrated that production of ROS may be required and beneficial for the normal and healthy muscular remodeling process (hypertrophy and mitochondrial biogenesis) to occur following a bout of exercise (80, 81, 148). Therefore, a delicate balance must be found with anti-inflammatory, antioxidant supplementation via an effective supplement post-exercise to help boost the antioxidant and anti-inflammatory systems when endogenous sources are not enough, but still promoting the positive aspects of ROS cellular-signaling.

NSAID Utilization Mechanism of Function and Theory

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that are commonly prescribed by a physician or taken over the counter by individuals in an attempt to help alleviate symptoms associated with exercise-induced muscle damage and restore proper muscle function (163). Typical NSAID examples currently on the market and used by consumers are ibuprofen, acetylsalicylic acid (aspirin), naproxen, diclofenac, flurbiprofen, and ketoprofen (77). The popularity of NSAID utilization is extremely high as exemplified in reports generated from the 2005 and 2010 National Health Interview Survey (NHIS). The NHIS report estimated that in 2010, approximately 43 million American adults (19.0%) took aspirin at least three times per

week for longer than 3 months (57% increase over 2005 estimates) and greater than 29 million American adults (12.1%) were NSAID regular users (41% increase over 2005 estimates) (209). The connection to the proposed research is based on the fact that regular NSAID utilization is heavily prevalent among athletes and recreationally active people engaging in vigorous forms of exercise (163, 202).

Expanding upon the initial discussion of muscle soreness and damage mechanisms, it is speculated that damage to skeletal muscle through strenuous activity or exercise leads to the activation of phospholipase A_2 (46, 163). Activation of this particular phospholipase enzyme cleaves arachidonic acid from the sarcolemma, causing cyclooxygenase (COX-1 and COX-2) enzymes to mediate production of prostaglandins (46, 163). As mentioned in the previous muscle soreness mechanisms discussion, prostaglandins, specifically, prostanoids, are released from the muscle cell as result of the now increasingly permeable sarcolemma to interact with surface cell receptors helping to sensitize local nerve endings to environmental changes as a result of the muscular injury in addition to influencing other biological functions (31, 46, 163). The primary NSAID mechanism of action according to the majority of the literature is based on the fact that NSAIDs reduce pain by inhibiting the activity of the COX pathway and thus the metabolism of arachidonic acid (31, 41, 68, 77, 163, 194).

While this NSAID mechanism of action seems to logically promote reduction of muscle pain and soreness, the inhibition of the COX pathway may also have additional downstream negative consequences such as downregulation of muscle protein synthesis and satellite cell proliferation. While much of the literature in this area remains

controversial, it is theorized that specific prostanoid receptors induce anabolic signaling following muscle damage through upstream stimulation of protein synthetic regulators (e.g. PI3K) (61, 163). Additional information in the literature also has determined that prostanoid-mediated communication through calcium-dependent pathways influences satellite cell proliferation mechanism in direct relation to increases in muscle fiber growth following muscle damage (74, 163). Thus, the inhibition of COX enzymatic activity through NSAID supplementation may theoretically promote positive effects on post-exercise muscle soreness, but could cause major anabolic deficiencies downstream particularly with regular, long-term NSAID use.

Antioxidant Vitamin Mechanism of Function and Theory

When antioxidants are most commonly described, many people and the majority of antioxidant research focuses on vitamin C (ascorbic acid) and vitamin E (tocopherol) (77), but there are numerous other endogenous and exogenous enzymatic and non-enzymatic antioxidants that act to protect against physiological injury caused by reactive oxygen species (ROS). Including vitamins C and E, there are many lesser known non-enzymatic endogenous antioxidants that exist in cellular components including glutathione, lipoic acid, carotenoids, uric acid, bilirubin, and ubiquinone (146). Some of the most widely researched enzymatic endogenous antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase of which both SOD and GPx are located in both muscular mitochondria and cytosol.

Despite vitamins C and E acting as endogenous antioxidants, the majority of antioxidant and certainly antioxidant vitamin research focuses on additional exogenous

vitamins C and E supplementation. Vitamins C and E are typically supplemented via an exogenous source when endogenous production is downregulated or inhibited in some capacity or when oxidant production levels overwhelm the endogenous antioxidant mechanisms (e.g. response to strenuous exercise bouts).

Vitamin E is a general class that contains several structural isomers of tocopherols and tocotrienols in which α-tocopherol is the most notable and potent antioxidant of the class (25, 85, 146). Considered a lipid soluble vitamin, vitamin E is typically associated with lipid-rich cellular components such as the mitochondria, sarcoplasmic reticulum, and the plasma membrane (146). Individuals with a consistently normal diet typically have relatively low tissue levels of vitamin E, but concentrations can be elevated with supplementation (85). Vitamin E is an important antioxidant due to its ability to downregulate superoxide, hydroxyl and lipid peroxyl radicals to their less active forms. Within the cellular membrane lipid bilayer, vitamin E also serves an integral role to break lipid peroxidation chain reactions (25, 146). Supplementation of vitamin E after strenuous bouts of exercise may be beneficial due to the fact that vitamin E tissue concentrations are significantly decreased under oxidative stress when the vitamin is converted to a radical during oxidant scavenging. Vitamin E can be converted back to its original state with the help of other antioxidants (e.g. vitamin C, glutathione) (146).

Vitamin C or ascorbic acid is perhaps the most well-known vitamin antioxidant as is part of the water-soluble class of vitamins. At physiological pH, vitamin C exists as ascorbate due to its lower pKa and is fairly ubiquitous across most tissues with

highest concentrations existing in the adrenal and pituitary glands (146, 208). Similar to the scavenging ability of vitamin E, vitamin C can serve as an oxidant scavenger for superoxide, hydroxyl and lipid hydroperoxide radicals. As previously mentioned, vitamin C also acts to recycle vitamin E back to its reduced state helping to protect the antioxidant system against free-radical and oxidative injury (146, 208). However, excessive amount of vitamin C can lead to negative consequences surrounding pro-oxidant effects in the presence of iron and copper due to their catalytic involvement in the production of free radicals (146, 208).

Phytochemical and Functional Food Mechanism of Action and Theory

As one of the primary phytochemical compounds contained within plant-derived fruits, vegetables, grains, legumes, teas, wines and coffee, polyphenols have demonstrated positive effects on many biological activities within the human system (14, 151). Polyphenols are defined by their chemical structure consisting of a characteristic aromatic ring with one or more attached hydroxyl groups that define their effective ability to act as free radical scavengers and metal chelators (14, 151). The general class of polyphenols can be divided into four subclasses: flavonoids, stilbenes, lignans, and phenolic acids, of which flavonoids are the most widely distributed (14, 151). Due to the large volume of various flavonoids, this subclass can be divided further into groups with specific common characteristics: flavonols, flavones, flavanols, isoflavones, anthocyanidins, and anthocyanins (151).

As a generally described series of functions for any antioxidant, classes of polyphenolic phytochemicals can reduce inflammation by acting directly as an

antioxidant or indirectly by promoting an increase in antioxidant gene or protein expression. The link between the production of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) to promote redox imbalance and subsequent oxidative stress and inflammatory gene expression is mediated by the ROS/RNS triggering of redox-sensitive kinases (14, 34, 151). Initially, apoptosis signal-regulating kinase 1 (ASK-1) is triggered to changes in the redox state that will lead to the downstream activation of mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF-κB), and activating protein-1 (AP-1) to influence inflammatory gene expression (34). The unique chemical structure of polyphenolic compounds defined by the high quantity of hydroxyl groups and associated aromatic rings allows this photochemical subclass to promote a strong antioxidant potential (14, 34, 151). In addition to their antioxidant chemical structure, polyphenols also have the capacity to affect the genetic expression and subsequent physiological levels of key antioxidant (and indirectly anti-inflammatory) enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) (14, 34, 151). According to recent literature, the increase in genetic expression of these antioxidant enzymatic pathways through polyphenol activation is carried out via the activation of the transcription factor nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2) (34, 151). Therefore, the reduction or down regulation of ROS and RNS in addition to other free radicals via introduction of the polyphenol subclass of phytochemicals will aid in maintenance of proper redox balance via attenuation of oxidative stress and in the end aid in the reduction of inflammation (34).

One of the major players in the upregulation of the body's inflammatory response is nuclear factor-kappa B (NF-κB) acting as an effector within the cytoplasm of a cell (14). Upon activation, the inhibitor proteins (IκB) associated with the NF-κB dimer are phosphorylated by IκB kinase, allowing the NF-κB dimer to translocate from the cytoplasm to the nucleus where it exerts an effect on gene expression, specifically transcription, to suppress cellular apoptosis, while initiating cellular transformation, proliferation, invasion metastasis, and inflammation (14, 66, 90, 161). NF-κB is redox transcription factor that is highly sensitive to redox stability/instability and can be readily activated by increases in inflammatory stimuli, most notably the production and release of pro-oxidative free radicals (161). A significant increase in ROS demonstrating a heightened state of physiological oxidative stress, favors expression of NF-κB to promote a greater stress and inflammatory response through the upregulation of genes that code for pro-inflammatory cytokines, chemokines, adhesion molecules, acute-phase proteins, immuno-receptors, and growth factors (14). Due to the linkage between oxidative stress and the inflammatory response mediated by NF-κB translocation, anti-inflammatory agents such as dietary polyphenols, have the potential to prevent, delay, or treat acute or chronic inflammation (69, 161). Polyphenol phytochemicals, through their anti-inflammatory properties, have been shown to modulate NF-κB activity by acting on multiple steps throughout the dimer activation process (151, 161). More specifically, interference with that IκB kinase rapid phosphorylation activity as the key control point in the NF-κB activation pathway seems,

based on the available literature, seems to be the point of effectiveness for polyphenol modulation of the NF-κB pathway (66, 69, 161).

The anti-inflammatory effects of polyphenols have various targets within the physiological system, but one of the most important targets is related to the arachidonic acid-dependent pathway. Inhibition of eicosanoids generating enzymes within this pathway such as: cyclooxygenases (COX), phospholipases (phospholipase A_2), and lipoxygenases, will aid in the reduction of prostranoid and leukotriene concentration (97, 161). Arachidonic acid release from membrane phospholipids is catalyzed by the cleavage of the phospholipase A_2 enzyme, at which point the resultant arachidonic acid will be catalyzed by either the cyclooxygenase (COX) or lipoxygenase (LOX) pathways as an important mediator in the inflammatory pathway, despite minimal pro-inflammatory effects at normal physiological levels in healthy humans (161, 206). Lipoooxygenases are enzymes defined by their ability to produce hydroxyl acid and leukotrienes from the aforementioned donation of arachidonic acid (121, 161). Cyclooxygenase exists in two major isoforms: COX-1 (expressed in a variety of tissues) and COX-2 (highly expressed in inflammatory-related cell types, particularly macrophages and mast cells post-pro-inflammatory cytokine stimulation, and is responsible for producing large amounts of prostalglandins) (3, 206). Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, irreversibly inhibit the activity of the COX-1 and COX-2 enzymes and the subsequent production of prostaglandins (e.g. PGE_2) at low, therapeutic doses (3). However, due to the lack of synthetic drug receptor binding control on a specific COX enzyme type within a specific area of the

physiological system, undesired or unknown side effects may result (161). Polyphenols, on the other hand, have been found to act as both an antioxidant and modulator of gene expression to exert their effect as COX-1 and COX-2 inhibitors at both the transcriptional and enzyme level (161). For example, previous research has demonstrated that COX-2 activity and gene expression was modified after consumption of polyphenols derived from red wine (e.g. resveratrol) and black tea (e.g. theaflavins) (108). Further, polyphenols derived from dietary sources have also been documented to inhibit both phospholipase A_2 (PL A_2) and lipoxygenase (LOX) enzymes in conjunction with COX to reduce arachidonic acid and the subsequent generation of prostaglandins and leukotrienes to exert anti-inflammatory effects on the arachidonic acid pathway (161, 206).

Tart Cherry Mechanism of Action and Theory

While cherries are typically considered sweet or sour (tart), there are more than 100 different cherry species (56). Sweet and sour cherries are typically characterized by their simple sugar quantities (e.g. fructose and glucose) and the presence of malic acid within tart cherries (42). Through extensive analysis, it has been determined in previous research that cherries contain both water and fat soluble vitamins, β-carotene, calcium, magnesium, phosphorous, potassium, and melatonin (in some types of tart cherries including Montmorency) (56). Tart cherries are particularly identified by greater quantities of vitamin A, vitamin C, β-carotene, and total polyphenols per 100 g weight of cherries. Both sweet and tart cherries contain a variety of polyphenols that include various cyanidins (e.g. anthocyanidins and anthocyanins), hydroxycinnamates, and

flavonols (e.g. catechins, epicatechins, and quercetins), of which tart cherries have greater concentrations of anthocyanins and hydroxycinnamic acids compared to sweet cherries (56, 96). The greater concentrations of these compounds in tart cherries bodes well compared to berry species as previous lipid membrane-based research determined that the activity of anthocyanins, cyanidins, and hydroxycinnamic acids derived from sweet and tart cherries is greater than other berries such as blackberries, red raspberries, blueberries, and strawberries, providing a rationale for potentially greater antioxidant effectiveness (56, 73).

Similar to the general polyphenolic anti-inflammatory mechanisms mentioned in the previous section, some of the active anti-inflammatory properties of cherry polyphenols have been hypothesized based on previous cherry research to specifically inhibit COX-II activity that is most closely replicated by ingestion of particular NSAIDs (e.g. ibuprofen and naproxen) at typical therapeutic dosages (126, 199). Previously described as one of the most active cherry anti-inflammatory components, previous in vitro studies have demonstrated that anthocyanins are able to inhibit production of a primary inflammatory mediator in macrophages, nitric oxide (NO) (126, 200). While NO is a gaseous free radial that beneficial in some physiological processes, production of NO by the inducible (iNOS) isoform has been proposed to be a major factor involved in pathological vasodilation and tissue damage due to its inflammatory provoking nature (14, 161, 206). More specifically, it has been postulated that multiple polyphenol compounds such as anthocyanins down regulate iNOS gene expression and lipopolysaccharide-induced NO production in macrophages through aforementioned

pathways of NF-κB inhibition (14, 88, 161, 206). Overall, the inflammatory inhibitory pathways demonstrated in all functional foods, particularly the large concentration of various polyphenols within tart cherries, serve to demonstrate the potentially positive health and exercise recovery benefits of supplementation in certain populations.

General Markers of Clinical Health

Effects of Tart Cherry Supplementation

Tart (e.g. Mortmorency) and sweet cherries (e.g. Bing) have received substantial attention within the clinical literature due to their high anthocyanin content (29, 30, 197) proven to aid in health (82, 93, 119, 188), inflammatory-related disease states (e.g. cardiovascular disease, diabetes, osteoarthritis, gout) (15, 82, 93, 119, 164), and sleep quality (75, 143). In a crossover study to determine the effect of a commercially available Montmorency tart cherry juice blend compared to a placebo on resistance to oxidative damage after acute stress, Traustadóttir et al. (188) employed a forearm ischemia/reperfusion (I/R) protocol on healthy, older adults across a 34-min time period at the end of the 14-d supplementation timeline. Traustadóttir et al. (188) measured capacity to resist oxidative damage through pre/post-forearm I/R changes in F_2-isoprostance levels and the accumulation of oxidative damage in short-lived (e.g. lipids) and long-lived (e.g. DNA and RNA) molecules excreted in the urine. This particular study found that supplementation with the tart cherry juice reduced the oxidative stress response and decreased long-term markers of oxidative damage in the urine. No difference was reported in short-term markers of oxidative damage in the urine (188).

Jacob et al. (82), studying a small cohort of healthy, young women, analyzed the pre/post-treatment effects of acute Bing sweet cherry consumption (280 g) on markers of inflammation over a 5-h period. The major finding by Jacob et al. (82) was that plasma urate levels significantly decreased over the 5-h post-consumption period with marginal decreases in plasma CRP and NO. In a very recent crossover study conducted by Bell et al. (11), a small cohort of healthy volunteers were supplemented for two days with two different doses (30 or 60 mL) of Montmorency tart cherry juice concentrate. Supporting the results reported by Jacob et al. comparing the pre/post-supplementation levels, Bell et al. (11) demonstrated a significant decrease in both serum urate and serum hsCRP as a result of tart cherry juice concentrate supplementation irrespective of dosage. In a second study looking at the consumption of Bing sweet cherries on plasma lipids and markers of inflammation to aid in reducing the risk of cardiovascular disease, Kelley et al. (93) treated a population of healthy men and women with 280 g/d of Bing sweet cherries for 28-d. Comparing pre/post-consumption concentrations over the 35-d study period, Kelley et al. (93) reported significantly decreased circulating concentrations of inflammatory markers hsCRP, NO, and RANTES (protein as a selective attractant for memory T-lymphocytes and monocytes). This results support those reported by Jacob et al. (82) and Bell et al. (11) in the acute treatment condition. However, sweet cherry consumption did not have any effect on total cholesterol, HDL, LDL, VLDL, fasting blood glucose, or insulin levels over the 28-d supplementation period (93). More recently, Schumacher et al. (164) supplemented a large cohort of otherwise healthy patients diagnosed with osteoarthritis (OA) of the knee with 473 mL/d of either a

Monmorency tart cherry juice blend or placebo for 6-wks. In support of the previous two inflammatory-related studies, Schumacher et al. reported a significant decrease in circulating hsCRP levels and improvements in both pain and function with tart cherry juice supplementation compared to placebo. Despite links to greater Western Ontario McMaster Osteoarthritis Index (WOMAC) scores with lower hsCRP levels, there was no difference between treatment groups with respect to WOMAC scores (164).

In another health aspect, Pigeon et al. (143) studied, in a crossover fashion, the effects of 2-wk Montmorency tart cherry juice blend supplementation compared to placebo on sleep enhancement in a small cohort of otherwise healthy older adults diagnosed with chronic insomnia. Pigeon et al. (143) found some beneficial effects on sleep for these participants with significant reductions in insomnia severity compared to placebo, but no improvements observed in sleep latency, total sleep time, or sleep efficiency compared to placebo. In a more comprehensive crossover sleep study, Howatson et al. (75) treated healthy men and women for 7-d with either a Montmorency tart cherry juice concentrate or placebo to observe differences in urinary melatonin levels and overall sleep quality. Unlike the pilot study conducted by Pigeon et al. (143), Howatson et al. (75) demonstrated that the tart cherry juice concentrate supplementation increased time in bed, total sleep time, and sleep efficiency compared to placebo. Further, total melatonin content as measured in the urine was significantly elevated upon tart cherry juice treatment compared to placebo, thus providing a potential rationale for improved sleep patterns in these healthy participants.

Muscle Pain or Soreness Perception in Response to Endurance Exercise

Effects of NSAIDs

Studying the effects of acute ibuprofen (8400 mg) ingestion against a placebo surrounding an eccentrically-based endurance bout in a crossover design study, Donnelly et al. (48) subjected young, healthy, and untrained male volunteers to a 45-min downhill treadmill run at 70% of their estimated maximum heart rate. Donnelly et al. (48) assessed muscle soreness before and after the downhill running bouts using a 10 point VAS scale for the front lower leg, back lower leg, front thigh, and back thigh/buttocks. Interestingly, the researchers also employed the same 10 point VAS scale for the measurement of soreness in response to a fixed amount of pressure with a spring-loaded probe on three sites (distal, proximal, and middle) within each aforementioned leg region (48). The overall muscle soreness response as derived from 20 soreness ratings found that leg muscle soreness significantly increased post-run, but no treatment effect was evident (48). However, when reviewing individual probe soreness measurements, ibuprofen supplementation corresponded to significantly greater post-run muscle soreness in the hamstring muscle group compared to placebo (48). In another crossover study with a similar design and subject cohort, Donnelley et al. (49) had volunteers supplement with diclofenac (50 mg) or a placebo 90-min before the previously described downhill running protocol and an additional 50 mg at 8-h intervals up to 72-h post-run. Employing the same subjective muscle soreness evaluation protocol as the previous study with three additional sites of measurement (abdomen, shoulders, and arms) for a total of 23 soreness values, Donnelley et al. (49) reported that overall muscle soreness

was unaffected by supplementation. Despite inconsistent effects on individual sites of muscle soreness, diclofenac tended to have an attenuating effect on muscle soreness in the middle of the hamstring muscle group compared to placebo (49).

Recruiting trained male and female ultramarathon runners competing in the 160 km Western States Endurance Run event, Nieman et al. (130) categorized athletes as NSAID users and non-users based on self-reported NSAID utilization during the race. The overwhelming majority of NSAID users supplemented with ibuprofen. In order to track DOMS, subjects were asked to record muscle soreness following the race and up to 7-d post-race using a 10-point Likert scale. NSAID use did not have any effect of DOMS over the post-race recovery. In a more recent study from the same research group, the effects of NSAID use in trained male and female ultramarathon runners on muscle injury and oxidative stress was studied by McAnulty et al. (115) who recruited a large cohort of runners competing in the 160 km Western States Endurance Run event. Similar to the earlier study by Nieman et al. (130), McAnulty et al. (115) categorized subjects based on their self-selected NSAID use over the course of the race. Muscle soreness ratings were recorded pre-race and up to 7-d post-race using a 10-point Likert scale. As previously described by Nieman et al. (130), McAnulty et al. (115) reported that there were no overall differences in DOMS between NSAID users and non-users despite significantly greater DOMS 1-d post-race in NSAID users versus non-users.

The consistency established with only two research groups primarily contributing to the literature in this category of NSAID effects on endurance performance provides confidence that the use of NSAIDs surrounding bouts of demanding, long duration

aerobic running activity does not aid in reducing post-run perceptions of muscle soreness. Further, this conclusion is commonly shared across both previously inactive and highly trained populations within these studies.

Effects of Antioxidant Vitamins

In an eccentrically breaking endurance trial where physically active subjects ran downhill continuously for 30-min and were acutely supplemented with either ascorbic acid or a placebo, Close et al. (37) reported no significant differences in VAS pain ratings or pressure algometry between groups up to 14-d post-exercise on six lower extremity locomotion muscle groups. With no effect on post-aerobic exercise delayed onset muscle soreness (DOMS) coupled with previous evidence in the literature, Close et al. (37) suggested a dissociation between post-exercise ROS production and DOMS. In an aerobic based crossover study designed to simulate multi-sprint sports, Thompson et al. (183) recruited habitually active males to ingest a vitamin C supplement (1 g dose) or a placebo 2-h prior to a 90-min intermittent shuttle-running test. The intensity of leg muscle soreness was rated on a 10-point VAS and Thompson et al. (183) reported that despite leg soreness increasing above baseline levels follow the LIST exercise bout, there were no differences in soreness ratings between supplement trials. Utilizing a similar muscle soreness protocol, in another placebo-controlled, running-based study, Thompson et al. (184) supplemented subjects with vitamin C or placebo for 14-d surrounding a prolonged 90-min high-intensity intermittent shuttle running test (LIST). Subjects were supplemented twice daily (morning and evening) with vitamin C (400 mg/d) or a placebo. Thompson et al. (184) determined that overall general soreness

tended to be greater in the placebo group, but was significantly greater in the placebo group compared to baseline and vitamin C group levels 24-h and 48-h post-exercise.

Despite two very different endurance-based running challenges of which one involved extra requirements for repetitive eccentric braking forces, both of the aforementioned studies concluded similarly to the NSAID published research. Based on these articles, antioxidant vitamin supplementation also does not seem to have any significant effect on post-run muscle soreness in physically active or trained subjects.

Effects of Tart Cherry Supplementation

The apparent beneficial effect of tart cherry juice or concentrate supplementation on the perception of muscle soreness after strenuous exercise bout is not standardized among published studies of varying modalities. In an endurance relay race-based study with trained runners (average running distance 26.3 km), Kuehl et al. (101) used a 100 mm VAS to track muscle pain and in subjects who ingested 710 mL of supplement for 8-d (7-d pre-race and day of race) surrounding the endurance challenge. Kuehl et al. (101) reported that treatment with the Montmorency tart cherry juice blend significantly reduced post-race pain compared to a placebo. Due to the relay nature of this particular endurance race, the time between race completion and muscle pain measurement in addition to individual subject running distance were not standardized across all participants (9). In another endurance running-based study, Howatson et al. (76) supplemented recreational marathon runners for a total of 8-d (5-d pre-race, day of race, and 2-d post-race) surrounding a marathon event with either 473 mL (237 mL am 237 mL pm) of a commercially available tart cherry juice blend or a placebo. Unlike the

results reported by Kuehl et al. (101), Howatson et al. (76) reported no difference in DOMS over the 48-h post-race period between tart cherry juice and placebo supplementation using a 200 mm VAS protocol. However, a baseline DOMS measurement was not conducted prior to supplementation. In a more recent aerobic exercise study, Bell et al. (13) supplemented trained cyclists with 60 mL (30 mL at 0800 and 30 mL at 1800) per day of Montmorency tart cherry concentrate or placebo for 7-d (4-d supplement loading pre-exercise and on each of the 3 trial days) prior to a 3-d bout of high intensity stochastic cycling. Using the same 200 mm VAS protocol reported by Howatson et al. (76), Bell et al. (13), reported similar results with no difference in DOMS ratings between Montmorency tart cherry supplementation and placebo up to 72-h post-exercise.

Unlike the consistency in results established among the NSAID and antioxidant vitamin research, the tart cherry endurance-based research provided conflicting reports of supplementation effectiveness in reducing perceptions of muscle soreness surrounding a bout of challenging endurance exercise. The lack of consistency in the literature with respect to tart cherry supplementation and endurance exercise is likely due to differences in method of muscle soreness perception measurement in addition to endurance exercise duration and modality (running versus cycling). Further, despite each of the studies sharing a similar over all supplement timeline (7-8 days), there was a large deviation in how the supplement ingestion was distributed pre- and post-exercise that may have likely contributed to the inconsistency in research findings.

Muscle Pain or Soreness Perception in Response to Resistance-Based Exercise

Effects of NSAIDs

Analyzing the effects ibuprofen supplementation over the course of 6-wk of contralateral biceps training, Krentz et al. (100) employed college-aged males and females with previous resistance training experience in this counter-balanced, double-blinded design. Subjects trained each arm on alternative days, 5-d/wk over the 6-wk training period in while they randomly received ibuprofen (400 mg/d) or a placebo immediately post-workout corresponding to arm training pattern. Muscle soreness was recorded for both arms every day over the training period using a 0-9 rating scale (0=no soreness, 9=intense soreness). Despite muscle soreness decreasing significantly from week 1 to week 2 of training, there was no significant change in soreness from weeks 2-6 or between the ibuprofen and placebo arms (100). The effects of ibuprofen supplementation on markers of muscle injury and performance following a bout of eccentrically-resisted arm curls were studied by Pizza et al. (145) in a crossover study using a small cohort of sedentary males. Pizza et al. (145) supplemented subjects with either ibuprofen (2400 mg/d) or placebo for a total of 15-d (5-d pre-exercise and 10-d post-exercise) surrounding a bout of 25 single arm, eccentrically-resisted arm curls. Muscle soreness was assessed using a 10-point VAS to rate perceptions during passive arm movement though full range of motion. Muscle tenderness was assessed on a total of 12 arm sites (5 upper arm and 7 forearm) using a metal probe paired with a load cell to find the point of tenderness (145). Pizza et al. (145) reported significantly greater muscle soreness and tenderness throughout the recovery period compared to pre-

eccentric exercise, but there was no difference demonstrated between treatments (145). In a similar study population of non-athletic males, Rahnama et al. (152) randomly assigned subjects to one of four study groups: physical activity, ibuprofen, physical activity + ibuprofen, or control. The 20-min of physical activity (warm-up) performed by the subjects prior to the eccentric arm exercise consisted of walking and jogging (5-min), hand and shoulder static stretching (10-min), and concentric movements with submaximal contractions (5-min). DOMS-inducing exercise involved performance of 70 eccentric arm-curl contractions 3-sec in duration at 80% MVC with 12-sec rest between eccentric repetitions. Ibuprofen ingestion occurred at 7 time points (400 mg/time point) over the study sequence, starting 1-h pre-eccentric exercise and ending 48-h post-eccentric exercise for a total of 2800 mg/d. Rahnama et al. (152) measured perception of muscle soreness using a 30-point scale (1=normal, 30=very, very sore) at full elbow extension. Muscle soreness increased significantly from baseline during the recovery and peaked in all groups 24-h post-eccentric exercise. As to be expected, the greatest soreness was recorded in the control group compared to the physical activity and combination groups at 24-h and 48-h post-eccentric exercise. Despite not being statistically significant, muscle soreness in the physical activity and combination groups was 27% and 23% lower than the ibuprofen only group 24-h post-eccentric exercise (152).

In an earlier resistance-based NSAID supplement study, Hasson et al. (72) employed healthy, untrained males and females to complete a 10-min bout of repeated bench step-ups with additional load of 10% body weight. Subjects were either

supplemented with 3 doses of ibuprofen (1200 mg) over 24-h starting 4-h pre-exercise (prophylactic), a single dose of ibuprofen (400 mg) at 24-h post-exercise (therapeutic), placebo, or a control receiving no treatment. Muscle soreness was determined on the anterior thigh at locations 2 cm apart using a metal probe (2 mm diameter tip) attached to a load cell and strain gauge with a gradually increasing force applied until subject discomfort was reached (72). The force associated with discomfort was applied up to 50 N of pressure. Hasson et al. (72) published that the primary areas of muscle soreness were concentrated around the distal head of the vastus medialis and proximal head of the vastus lateralis. More specifically, soreness perception for the prophylactic ibuprofen group was approximately 50% of that noted in all other groups 24-h post-exercise. Quadriceps soreness perception was also significantly less at 48-h post-exercise in both ibuprofen supplementation groups compared to placebo and control (72).

As previously noted, muscle soreness and pain perception significantly increased over baseline levels in all study groups as a result of upper or lower body eccentrically-resisted exercise. Ibuprofen supplementation did not seem to have any effect on attenuating a post-exercise increase in muscle soreness following upper body involved exercise. However, based on the results described by Rahnama et al. (152), it seems as though muscular activation through implementation of a warm-up protocol prior to the exercise is more effective than ibuprofen supplementation to aid in reduction of post-upper body resistance exercise muscle soreness. Contrarily, cutting the acute ibuprofen dosage in half surrounding a bout of lower body resistance-based exercise, results seem to conflict greatly with those mentioned previously following upper body resistance-

based exercise. With no basis of study comparison, Hasson et al. (72) published data indicating that post-resistance exercise soreness was reduced by 50% with acute, prophylactic ibuprofen supplementation compared to therapeutic ibuprofen ingestion, placebo, and control. However, differences in all of these studies could lie in the method of soreness perception measurement, as Hasson et al. (72) used application of pressure coupled with a strain gauge as opposed to a simple VAS implemented in other studies.

Effects of Antioxidant Vitamins

Healthy, non-resistance trained men, were recruited by Beaton et al. (8) to participate in a placebo-controlled study where subjects were supplemented for 30-d with either vitamin E (1200 IU/d) or a placebo. Within this particular study, subjects performed an isokinetic protocol that compromised of 24 sets of 10 eccentrically-resisted knee extension/flexion contractions (8). Beaton et al. (8) employed the Descriptor Differential Scale (DDS) (110) to assess the intensity and unpleasantness of muscle soreness as a result of the eccentric exercise bout. As a result, Beaton et al. reported no differences in intensity and unpleasantness of muscle soreness between the supplementation groups (8). In another cohort of healthy, untrained males, Bryer and Goldfarb (22) supplemented subjects for 18-d (14-d pre-exercise and 4-d post-exercise) three times daily with either vitamin C (3 g/d) or a placebo. Bryer and Goldfarb (22) had subjects perform 70 eccentrically-resisted elbow flexions on the non-dominant arm with 10-sec rest allotted between repetitions. The degree of elbow flexor muscle soreness was determined using a 10 point VAS in both a resting state and in response to palpation. As a result of the eccentric exercise protocol, muscle soreness was

significantly greater than baseline in both groups across the 96-h recovery period (22). However, supplementation with vitamin C significantly attenuated muscle soreness in the non-dominant arm compared to placebo immediately, 4-h, and 24-h post-eccentric exercise (22).

In an earlier eccentrically-based upper body exercise study, Childs et al. (32) supplemented previously untrained subjects with either a placebo or a vitamin C (12.5 mg/kg body weight) + N-acetyl-cysteine (NAC) (10 mg/kg body weight) combination for 7-d after the exercise challenge. As the exercise protocol, subjects were asked to perform 3 sets of 10 repetitions of eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. Unlike the results reported by Bryer and Goldfarb (22), supplementation with the antioxidant cocktail did not have any effect on increases in post-exercise muscle pain compared to placebo, despite an increase in muscle pain up to 2-d post-exercise. Supplementing moderately active and healthy male volunteers for 37-d with a combination of vitamin C (500 mg/d) and vitamin E (1200 IU/d) or a placebo, Shafat et al. (167) employed an exercise protocol comprised of 30 sets of 10 eccentric knee extensions on their dominant leg using an isokinetic dynamometer. Shafat et al. (167) evaluated leg muscle soreness using a 10 point VAS on a total of 8 upper leg sites (anterior and posterior) and determined that the antioxidant vitamin combination did not change the time course of muscle soreness in the exercise recovery period.

Similar to the perception of muscle soreness results described by NSAID research, the use of antioxidant vitamins also provided some uncertainly with respect to

effectiveness of supplementation on muscle soreness. The majority of the aforementioned antioxidant vitamin research published results that indicated no effectiveness of ingestion on perception of muscle soreness following eccentrically-based resistance exercise compared to a placebo. However, as the only study that did not use a combination of antioxidant vitamins as part of the supplementation regimen, Bryer and Goldfarb (22) asked subject to ingest a large quantity of vitamin C (compared to the dosage strategies of other studies) over the course of 18-d that may have contributed to the supplement's effectiveness in significantly attenuating post-exercise muscle soreness. The supplement time table, exercise modality and volume, method of soreness perception, and study population utilized by Bryer and Goldfarb (22) are not much different than other similar studies, thus pointing to the supplement itself as the likely contributor to different results.

Effects of Phytochemicals and Functional Foods

In an acute eccentric exercise-based crossover study, Trombold et al. (189) recruited recreationally active males who were supplemented twice daily with either a pomegranate juice (960 mL/d) or a placebo (960 mL/d) over a 9-d period (4-d pre-exercise, day of, and 4-d post-exercise) surrounding the eccentric exercise workout. The single eccentric exercise session involved two sets of 20 maximal eccentric elbow flexions in which subjects were required to resist an isokinetic dynamometer for 3-sec followed by a 15-sec rest per repetition (189). The degree of elbow flexor muscle soreness was determined using a 10 point VAS. Over the course of the exercise recovery, Trombold et al. (189) found significantly attenuated muscle soreness 2-h post-

exercise as a result of pomegranate juice supplementation versus placebo, but did not detect any other significant differences in ratings of muscle soreness between the two supplementation groups over the 96-h recovery period. In a more recent pomegranate juice supplementation study, Trombold et al. (190) supplemented resistance-trained men surrounding a single workout of both unilateral resisted eccentric elbow flexion and knee extension exercises. Subjects were supplemented twice daily with either a pomegranate juice (500 mL/d) or a placebo (500 mL/d) over a 15-d period (7-d pre-exercise, day of, and 7-d post-exercise) surrounding the exercise bout (190). The single eccentric exercise bout involved three sets of 20 maximal eccentrically resisted elbow flexions on an isokinetic dynamometer and six sets of 10 unilateral eccentrically resisted (3-sec count) knee extensions at 110% unilateral 1-RM on a traditional isotonic leg extension machine (190). The degree of elbow flexor and leg extensor muscle soreness was determined using a 10 point VAS. Unlike the previous study conducted by Trombold et al. (190), elbow flexion soreness was significantly attenuated over the 168-h exercise recovery period in the supplement group with notable group differences at 48-h and 72-h post-exercise. Despite an increase in knee extensor muscle soreness throughout the 168-h recovery period, there were no significant differences between groups reported (190).

In another study using eccentric exercise as a mechanism of muscular injury, Goldfarb et al. (65) supplemented subjects with a proprietary blend of fruit, vegetable, and berry powder concentrates over 28-d prior to the exercise bout and 4-d after. This propriety blend of fruit, vegetable, and berry powder concentrates provided a source of β-carotene (7.5 mg/d), vitamin C (276 mg/d), and vitamin E (108 IU/d), in addition to a

natural source of flavonoids and anthocyanins (65). The structure of the study required subjects to perform an exercise bout consisting of four sets of 12 repetitions of eccentrically resisted elbow flexions on the non-dominant arm at 20°/sec angular velocity surrounded by sets of MVICs to assess muscular strength. A 10 point VAS was used to assess muscle soreness through a full range of motion and in response to palpation (65). Over the 72-h recovery period, both supplementation groups demonstrated similar increases in muscle soreness, peaking at 24-h post-eccentric exercise, but no group difference was reported at any time point (65). In an fourth study examining the effects of eccentrically-resisted elbow flexions, Phillips et al. (142) treated untrained subjects with either a placebo or mixed functional food-derived antioxidant supplement for 14-d (7-d pre-exercise and 7-d post-exercise). The mixed functional food supplement consisted of mixed tocopherols (300 mg/d), DHA, (800 mg/d), and flavonoids (100 mg/d hesperetin and 200 mg/d quercetin). Subjects were asked to perform 3 sets of 10 repetitions of eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. Similar to the protocol used by Goldfarb et al. (65), a 10 point VAS was used to assess muscle soreness in response to palpation and full range of motion movement. Phillips et al. (142) reported that despite a significant increase in pain perception at 72-h post-exercise, there was no significant differences between the responses of the treatment groups throughout the entire 7-d recovery period.

Examining intramuscular adaptations to a single bout (100 repetitions: 10 sets of 10 repetitions) of eccentrically-resisted isokinetic leg extensions on the dominant leg, Kerksick et al. (94) supplemented active males for 14-d with either *N*-acetyl-cysteine

(NAC) (1,800 mg/d), epigallocatechin gallate (EGCG) (1,800 mg/d), or a placebo. Perception of muscle soreness was assessed using a 10 cm VAS scale (94). Compared to baseline perceptions, muscle soreness was significantly greater 6-h, 24-h, 48-h, and 72-h post-exercise with placebo supplementers revealing a significantly greater soreness level at 24-h post-exercise compared to ECGC and NAC groups.

After a careful review of this research segment, there is no clear evidence to support or refute the use of certain phytochemicals or functional foods to help reduce perceptions of muscle soreness following bouts of resistance-based exercise. Even when sorting the research based on upper or lower body exercise, conflicting reports still exist as to the effectiveness of these supplements as a general class with respect to effectiveness in reducing perceptions of muscle soreness. The lack of conclusive evidence mostly likely stems from the large variety of supplements utilized across all studies represented within this subsection. However, even between two studies conducted by the same research group on similar study cohorts, utilizing the same pomegranate juice supplement, Trombold et al. reported conflicting reports between the two studies.

Effects of Tart Cherry Supplementation

In an eccentric resistance-based crossover study, Connolly et al. (40) supplemented healthy, college-aged males with 710 mL (355 mL am and 355 mL pm) of a Montmorency tart cherry juice blend or a placebo for 8-d (3-d pre-eccentric, day of eccentric, and 4-d post-eccentric exercise) surrounding a bout of eccentric elbow flexion contractions. As a result of this exercise and supplementation protocol, Connolly et al.

(40) reported that consumption of a Montmorency tart cherry juice blend in healthy college-aged males significantly reduced pain in the elbow flexors after a bout of eccentric exercise using a visual analog scale (VAS). Peak muscle pain was achieved 24-h post-exercise in the tart cherry group compared to a continued increase in pain 48-h post-exercise in the placebo group. In contrast, Connolly et al. (40), using a standard manual muscle myometer, reported no difference in pressure pain threshold (PPT) scores between the two experimental groups. In a second resistance-based crossover study, Bowtell et al. (20), employed a strenuous single leg knee extension protocol in a cohort of well-trained male athletes in conjunction with 60 mL (30 mL am and 30 mL pm) per day of Montmorency tart cherry concentrate or placebo for 10-d (7-d pre-exercise, day of exercise, and 2-d post exercise), closely resembling the supplementation protocol employed by Bell et al. (10). Bowtell et al. (20) demonstrated a trend in post-exercise muscle pain reduction via PPT (pain-pressure threshold) using an algometer with Montmorency tart cherry juice supplementation up to 48-h post-exercise compared to placebo.

With only two research studies employing resistance-based exercise and tart cherry supplementation, it is difficult to make any conclusions from the evidence presented. These two studies are very different from one another as one used upper body resistance-based exercise and the other lower-body. Further, the supplements ingested by the subjects across the two studies is also different as one is a juice blend and the other is a concentrate despite having a similar supplementation duration. At this point, evidence is inconclusive based on pain pressure threshold (PPT) measurements

taken surrounding a single bout of resistance-based exercise and short-term supplementation of a tart cherry supplement.

Muscle Catabolic and Secondary Muscle Damage Response to Endurance Exercise

Effects of NSAIDs

In an endurance-based crossover study examining the effects of acute ibuprofen (8400 mg) ingestion surrounding an eccentrically-based endurance bout, Donnelly et al. (48) subjected young, healthy, and untrained male volunteers to a 45-min downhill treadmill run at 70% of their estimated maximum heart rate. Donnelly et al. (48) reported an increase in serum CK, AST, and lactate dehydrogenase following the downhill running protocols with maximal activity of CK and AST occurring at 24-h post-run, while lactate dehydrogenase, creatinine, and urea peaked 6-h post-run. The results of the study revealed that both serum CK and urea levels were significantly higher after ibuprofen supplementation compared to placebo throughout the post-downhill run recovery (48). In another crossover study with a similar design and subject cohort, Donnelley et al. (49) required volunteers to supplement with diclofenac (50 mg) or a placebo 90-min before the previously described downhill running protocol and an additional 50 mg every 8-h up to 72-h post-run. Serum peaks of all markers measured were identical to the previously mentioned study, but the results of this study revealed that there were no differences in serum biochemical markers of muscle damage or catabolism between diclofenac and placebo supplementation (49).

Recruiting trained male and female ultramarathon runners competing in the 160 km Western States Endurance Run event, Nieman et al. (130) categorized athletes as

NSAID users and non-users based on self-reported NSAID utilization during the race. The overwhelming majority of NSAID users supplemented with ibuprofen. Measuring serum creatine phosphokinase (CPK) as an indicator of muscle damage, Nieman et al. (130) found no differences in plasma CPK levels in NSAID users versus non-users throughout the post-exercise period. McAnulty et al. (115) also recruited a large cohort of runners competing in the 160 km Western States Endurance Run event to study the effects of NSAID supplementation and categorized them based on their self-selected NSAID use over the course of the race. Muscle damage was assessed by McAnulty et al. (115) through measurement of serum CPK and similar to previous findings by Nieman et al. (130), research also reported no differences in plasma CPK levels between NSAID users and non-users over the course of the 7-d protocol (115).

The endurance-based research listed in this section should be considered fairly reliable and consistent as both sets of 2 studies utilized the same exercise protocol and similar study populations. One of study sets consisted of two pieces of supplement intervention research that utilized healthy, but untrained subjects to complete a highly intense eccentrically-based endurance workout. While one study found negative effects of ibuprofen supplementation, the other study did not find any difference between another NSAID, diclofenac, when compared to a placebo. Similar to the study involving diclofenac supplementation, two additional ultramarathon studies utilizing a non-supplementation intervention protocol reported similar ineffective results in highly trained endurance runners. Based on this research, no positive effects of NSAID

ingestion surrounding bouts of intense endurance exercise were published with respect to attenuating post-exercise muscle damage.

Effects of Antioxidant Vitamins

In an aerobically based study conducted by Kang et al. (89), researchers compared a polyphenol-rich extract derived from litchi fruit (OLFE), a vitamin C (800 mg/d) + vitamin E (1200 IU/d) combination, and a placebo on outcomes of endurance performance capacity following 30-d of supplementation in healthy, recreationally trained endurance subjects. The vitamin combination (C + E) demonstrated a 4-fold increase in LDH response following exercise 30-d after supplementation compared to baseline measures, while the OLFE and placebo groups demonstrated a decrease in post-exercise LDH response following 30-d of supplementation (89). Analyzing only an antioxidant vitamin combination, Peterson et al. (140), supplemented male recreationally-trained runners with either an vitamin C (500 mg/d) + vitamin E (400 mg/d) combination or a placebo for 14-d before and 7-d after a 90-min treadmill run at a 5% decline and 75% VO_2 max. As a result of the eccentrically-braked endurance running challenge, Peterson et al. (140) reported a 6-fold increase in plasma CK levels 24-h post-exercise with no differences exhibited by supplementation.

Attempting to simulate multi-sprint sports, Thompson et al. (183) recruited habitually active males within a crossover design study to ingest a vitamin C supplement (1 g dose) or a placebo 2-h prior to a 90-min intermittent shuttle-running test. As measures of muscle damage, Thompson et al. (183) reported that serum CK and AST activity increased above baseline levels during and after the 90-min LIST exercise. AST

activity peaked immediately post-exercise but remained elevated above baseline 72-h post, while CK levels peaked 24-h post-LIST and returned to baseline levels by the end of the testing protocol (72-h) with no differences reported between supplementation treatments (183). Thompson et al. (184) supplemented subjects with vitamin C or placebo for 14-d surrounding a prolonged 90-min high-intensity intermittent shuttle running test (LIST). Subjects were supplemented twice daily (morning and evening) with vitamin C (400 mg/d) or a placebo. As a result of the differences in supplementation, Thompson et al. (184) reported that serum CK levels increased and returned to baseline values at 72-h of recovery similarly in both groups as a result of the LIST exercise challenge. As another marker of muscle damage, plasma myoglobin concentrations peaked 1-h post-exercise and remained above baseline values through 24-h of recovery, irrespective of supplementation groups. Vassilakopoulos et al. (105) supplemented healthy, non-athlete volunteers with an antioxidant combination (60-d of vitamins A, C, and E; 15-d of allopurinol; and 3-d of *N*-acetylcysteine) prior to a 45-min bout of cycling at 70% VO_2 max. Blood samples were drawn at baseline, immediately, 30-min, and 120-min post-exercise. Vassilakopoulos et al. (105) reported no post-exercise change in plasma CK level up to 24-h of recovery as a result of the exercise bout or antioxidant cocktail supplementation.

Despite various supplementation and endurance exercise challenges, the consensus of all research described in this section is that supplementation with an antioxidant vitamin or vitamin combination does not provide any more benefit than a placebo in reducing markers of muscle damage. The study by Kang et al. (89)

demonstrates a detrimental effect of antioxidant supplementation as LDH levels increased significantly post-exercise after 30-d of supplementation compared to post-exercise levels at baseline, whereas the opposite pattern was demonstrated in the placebo and OLFE supplementation groups.

Effects of Phytochemicals and Functional Foods

In an endurance-based study, Pilaczynska-Szczesniak et al. (144) recruited male members of the Polish rowing team to ingest 150 mL/d (3x 50 mL) of chokeberry juice or placebo over the course of their 4-wk training camp. At the beginning and end of the training camp, the crew athletes performed a 2000-m rowing test followed by an incremental rowing session after 1-d rest with 3-min stages of increasing intensity and 30-sec recovery between intervals (144). Hematological testing by Pilaczynska-Szczesniak et al. (144) showed significantly lower CK levels in the chokeberry supplemented rowers compared to placebo at 1-min post-incremental test. In another placebo-controlled study utilizing a cohort of highly trained male rowers of the Polish national team, Skarpanska-Stejnborn et al. (169) supplemented similar athletes with artichoke-leaf extract (1,200 mg/d) or a placebo 3 times per day for 5-wk. Skarpanska-Stejnborn et al. (169) required subjects to perform a 2,000 m maximum-effort test on a rowing ergometer as the exercise performance intervention with blood samples drawn pre-exercise, 1-min, and 24-hr post-exercise. Supplementation did not have any effect on CK levels following 5-wk of ingestion. In a more recent study within the same rowing athlete population, Skarpanska-Stejnborn et al. (168) supplemented subjects with *Rhodiola* rosea extract (200 mg/d) or a placebo 2 times per day for 4-wk. Following the

same maximal rowing test and blood sample timeline, Skarpanska-Stejnborn et al. (168) reported similar results to the previous study with no supplementation effect on plasma CK levels.

Lafay et al. (102) employed a crossover design study with a variety of elite male sportsman to investigate the effects of a polyphenol-rich grape extract (400 mg/d) compared to placebo (400 mg/d) supplementation over a 30-d training and competition period. In measurement of creatine phosphokinase (CPK) as a biomarker of skeletal muscle damage, Lafay et al. (102) demonstrated no significant differences between groups or within groups across the 30-d supplementation and training period. Another aerobically based study conducted by Kang et al. (89) compared a polyphenol-rich extract derived from litchi fruit (OLFE), a vitamin C + vitamin E combination, and a placebo on outcomes of endurance performance capacity following 30-d of supplementation in healthy, recreationally trained endurance subjects. Kang et al. (89) described a stark difference in lactate dehydrogenase (LDH) response patterns following an incremental treadmill VO_2 max test as OLFE attenuated the post-exercise LDH response after 30-d of supplementation compared to levels at baseline testing and patterns reported by antioxidant vitamin and placebo supplementers. Interestingly, in a crossover design study conducted in trained cyclists by Morillas-Ruiz et al. (125), subjects performed a 90-min submaximal endurance time trial at 70% VO_2 max on a cycle ergometer while consuming a commercial antioxidant beverage containing fruit concentrates and carbohydrates over the testing protocol. Morillas-Ruiz et al. (125) reported that CK levels increased significantly immediately post-exercise with no

difference between groups. LDH levels did not increase over pre-exercise levels and no differences were found between groups.

The effects of phytochemical or functional food supplementation surrounding bouts of challenging endurance exercise are inconclusive with regards to attenuation of the rise in post-exercise serum markers of muscle damage. While the first three studies were conducted by the same research group within a similar study cohort and under nearly identical training conditions, only the chokeberry juice compared to the two extract supplements demonstrated an enhanced effect on post-exercise CK levels. It could be concluded that the polyphenol-rich chokeberry juice likely has a positive effect on the secondary effects resulting from the initial physiological muscle damage as a result of repetitive muscular contraction. With its high polyphenol polymer content, antioxidant capacity, and bioavailability, OLFE supplementation in the study conducted by Kang et al. (89) further supported the chokeberry juice results. However, supplementing with another polyphenol-rich supplement, grape extract, Lafay et al. (102) did not find any significant differences compared to a placebo. This may be due to the variety of athletes supplemented in this study or a lower bioavailability of grape-extract compared to OLFE. Overall, it seems that there may be some promising advantages of supplementation with natural sources of polyphenol or catechin-rich antioxidants following bouts of endurance exercise on the secondary muscle damage response.

Effects of Tart Cherry Supplementation

Bell et al. (13) in an acute endurance study following a combination of cycling sprints and time trial over a 109-min period that was repeated over three consecutive days, demonstrated a small mean increase in creatine kinase (CK) across the trial period, but no differences between Montmorency tart cherry concentrate and placebo supplementation. Unlike the unloaded cycling study conducted by Bell et al. (13), Howatson et al. (76), following marathon running demonstrated a trend of lower post-resistance exercise creatine kinase (CK) levels when supplementing with tart cherry juice compared to placebo up to 48-h of post-marathon recovery. Following a treadmill incremental exercise protocol with thoroughbred horses, Ducharme et al. (50) also reported a trending attenuation in CK levels during exercise recovery when supplementing with a tart cherry juice blend compared to placebo. As a secondary marker of muscle damage and stress, Ducharme et al. (50) reported that AST was significantly mitigated during and following the incremental exercise protocol in the tart cherry-treated horses compared to placebo (9).

Interestingly, two of the three tart cherry supplementation studies involved biomechanically loaded running compared to a cycling activity. The running-based research also both supplemented subjects with a tart cherry juice beverage compared to the unloaded cycling study that supplemented cyclists with a tart cherry concentrate. Both running studies supplementing subjects with tart cherry juice, similar to the previously mentioned chokeberry-juice supplementation study, demonstrated beneficial effects on post-exercise attenuation of serum markers of muscle damage compared to a

placebo. Contrastingly, the unloaded cycling study having subjects ingest a tart cherry concentrate did not find any significant difference in muscle damaging effects when compared to supplementing with a placebo. Without a direct comparison of supplements across both aerobically-based exercise challenges, it is difficult to attribute the cause of result differences. However, the tart cherry juice as part of the entire polyphenolic juice-based supplementation class exhibits positive effects worth exploring in future research.

Muscle Catabolic and Secondary Muscle Damage Response to Resistance Exercise

Effects of NSAIDs

The effects of ibuprofen supplementation on markers of muscle injury and performance following a bout of eccentrically-resisted arm curls were studied by Pizza et al. (145) in a crossover study using a small cohort of sedentary males. Pizza et al. (145) supplemented subjects with either ibuprofen (2400 mg/d) or placebo for a total of 15-d (5-d pre-exercise and 10-d post-exercise) surrounding a bout of 25 single arm, eccentrically-resisted arm curls. As a marker of muscle injury, Pizza et al. (145) reported significantly lower serum CK levels at 3-d post-eccentric exercise with ibuprofen supplementation compared to placebo with a significant increase in serum CK levels from baseline and pre-exercise in both treatments at 2-d, 3-d, and 4-d of recovery. In a placebo-controlled fashion, Rahnama et al. (152) randomly assigned non-athletic male subjects to one of four study groups: physical activity, ibuprofen, physical activity + ibuprofen, or control. The physical activity groups performed 20-min of warm-up activity prior to the eccentric exercise. DOMS-inducing exercise involved performance of 70 eccentric arm-curl contractions 3-sec in duration at 80% MVC with 12-sec rest

between eccentric repetitions. Ibuprofen ingestion occurred at 7 time points (400 mg/time point) over the study sequence, starting 1-h pre-eccentric exercise and ending 48-h post-eccentric exercise for a total of 2800 mg/d. Following the eccentric exercise bout, Rahnama et al. (152) showed an increase in serum CK levels across all groups. CK activity was significantly greater in the control group compared to all of the other supplementation groups across most recovery time points, however CK activity was also higher in the ibuprofen group compared to the physical activity group at 48-h post-eccentric exercise.

In an earlier resistance-based NSAID supplement study, Hasson et al. (72) employed healthy, untrained males and females to complete a 10-min bout of repeated bench step-ups with additional load of 10% body weight. Subjects were either supplemented with 3 doses of ibuprofen (1200 mg) over 24-h starting 4-h pre-exercise (prophylactic), a single dose of ibuprofen (400 mg) at 24-h post-exercise (therapeutic), placebo, or a control receiving no treatment. As a marker of muscle damage, serum CK levels were significantly elevated above baseline levels 24-h and 48-h post-exercise, but unlike the results reported by Pizza et al. (145), Hasson et al. (72) did not find any post-exercise difference between treatments.

While all three aforementioned resistance-based studies supplemented subjects with ibuprofen, each of the authors published differing results. Pizza et al. (145) described a positive effects of ibuprofen supplementation on serum CK levels compared to equivocal and negative impacts reported in the other two studies. The most effects of ibuprofen supplementation may likely be attributed to the longer supplementation

period, more specifically, ingestion throughout the extended recovery period up to 10-d post-exercise. Despite some differences in exercise modalities, two studies utilized similar upper body eccentrically-based resistance protocols with congruent subject cohorts. There does not seem to be any conclusive evidence with NSAID supplementation and effects on markers of markers of muscle damage surrounding a single bout of intense resistance exercise.

Effects of Antioxidant Vitamins

Healthy, non-resistance trained men, were recruited by Beaton et al. (8) to participate in a placebo-controlled study where subjects were supplemented for 30-d with either vitamin E (1200 IU/d) or a placebo. Within this particular study, subjects performed an isokinetic protocol that compromised of 24 sets of 10 eccentrically-resisted knee extension/flexion contractions (8). Over the 7-d post-eccentric exercise recovery period, serum CK levels increased over baseline levels and remained significantly greater than baseline at day 7 (8). There was a significantly greater elevation in serum CK levels 3-d post-eccentric exercise in the placebo group compared to the vitamin E supplemented group, but CK levels were once again similar between groups at recovery day 7 (8). In another cohort of healthy, untrained males, Bryer and Goldfarb (22) supplemented subjects for 18-d (14-d pre-exercise and 4-d post-exercise) three times daily with either vitamin C (3 g/d) or a placebo. Bryer and Goldfarb (22) had subjects perform 70 eccentrically-resisted elbow flexions on the non-dominant arm with 10-sec rest allotted between repetitions. Plasma CK activity was greater than baseline levels 48-h, 72-h, and 96-h post-eccentric exercise in both groups with a trend of vitamin C

supplementation attenuating the CK response during that same recovery time period compared to placebo (22).

In an earlier eccentrically-based upper body exercise study, Childs et al. (32) supplemented previously untrained subjects with either a placebo or a vitamin C (12.5 mg/kg body weight) + N-acetyl-cysteine (NAC) (10 mg/kg body weight) combination for 7-d after the exercise challenge. As the exercise protocol, subjects were asked to perform 3 sets of 10 repetitions of eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. Blood was drawn pre-exercise, days 2, 3, 4, and 7 following the exercise bout. Childs et al. (32) reported that plasma CK and LDH in addition to serum myoglobin were elevated on days 2, 3, and 4 following exercise with plasma CK and LDH levels higher in the antioxidant supplementation group compared to placebo. Contrarily, serum myoglobin levels tended to be lower in the antioxidant supplemented group compared to placebo.

All three studies involved some variation of eccentrically-resisted elbow flexion movements in untrained subjects. Supplementing with a single antioxidant vitamin (vitamin C or E) for approximately 3-4-wks prior to the resistance exercise challenge proved to be effective in attenuating the post-exercise rise in serum markers of muscle damage compared to a placebo. Results in the last study mentioned conducted by Childs et al. (32) likely produced inconsistent results due to the lack of pre-exercise supplementation and the significantly lower exercise volume compared to the other two studies described in this section. Further, the supplementation combination of vitamin C and NAC may have been another cause of varied results. Future research with

resistance-based exercise and antioxidant vitamin supplementation likely needs to compare multiple antioxidant vitamins and combinations within the same study to start painting a clearer picture of the overall effects of supplementation on muscle damage markers.

Effects of Phytochemicals and Functional Foods

Utilizing a crossover study design, Trombold et al. (189) recruited recreationally active males to supplement twice daily with either a pomegranate juice (960 mL/d) or a placebo (960 mL/d) over a 9-d period (4-d pre-exercise, day of, and 4-d post-exercise) surrounding a single workout involving two sets of 20 maximal eccentrically-resisted elbow flexions. Trombold et al. (189) measured serum CK and myoglobin as markers of muscle damage, but found no significant differences between supplementation groups despite increased levels of both markers above baseline levels over the course of the 96-h recovery period. Representing a longer supplement timeline, Goldfarb et al. (65) recurited healthy, college-aged males to ingest a fruit, berry, and vegetable concentrate or placebo twice daily for 4-wks (28-d pre-eccentric exercise, day of, and 4-d post-eccentric exercise). This propriety blend of fruit, vegetable, and berry powder concentrates provided a source of β-carotene (7.5 mg/d), vitamin C (276 mg/d), and vitamin E (108 IU/d), in addition to a natural source of flavonoids and anthocyanins (65). Subjects were required to perform an eccentric exercise bout of eccentrically resisted elbow flexions surrounded by sets of MVICs to assess muscular strength (65). Goldfarb et al. (65) reported increases in serum CK levels 24-h to 72-h post-eccentric exercise, but the pattern of change was similar between groups.

In an third study examining the effects of eccentrically-resisted elbow flexions, Phillips et al. (142) treated untrained subjects with either a placebo or mixed functional food-derived antioxidant supplement for 14-d (7-d pre-exercise and 7-d post-exercise). The mixed functional food supplement consisted of mixed tocopherols (300 mg/d), DHA, (800 mg/d), and flavonoids (100 mg/d hesperetin and 200 mg/d quercetin). Subjects were asked to perform 3 sets of 10 repetitions of eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. Serum LDH and CK levels demonstrated significant increases above baseline values 72-h post-exercise and a decrease to baseline levels at 7-d of recovery. No differences between treatment groups were reported. Phillips et al. (142) reported a similar pattern in plasma AST and ALT (markers of secondary muscle damage and renal stress) between treatments that followed a 72-h post-exercise peak with a congruent marker fall to day 7 of recovery where levels remained elevated above baseline. Examining intramuscular adaptations to a single bout (100 repetitions: 10 sets of 10 repetitions) of eccentrically-resisted isokinetic leg extensions, Kerksick et al. (94) supplemented active males for 14-d with either *N*-acetyl-cysteine (NAC) (1,800 mg/d), epigallocatechin gallate (EGCG) (1,800 mg/d), or a placebo. There were no significant differences in serum markers of muscle damage (CK and LDH) across supplementation groups, however, CK was significantly elevated over baseline levels at 6-h, 24-h, and 48-h post-exercise, while LDH peaked 6-h post-exercise.

Through a multitude of various phytochemical and functional food supplements likely to contain differing levels and combinations of antioxidants and polyphenolics, all

of the literature relating to supplementation surrounding a bout of resistance-based exercise concluded that ingestion did not have any greater attenuating effect over a placebo on post-exercise markers (primary and secondary) of muscle catabolism. Research results were also consistent across both upper and lower body resistance-based exercise modalities.

Effects of Tart Cherry Supplementation

In a resistance-based exercise study, Bowtell et al. (20), following exhaustive leg extension exercise, reported trends for greater total serum CK activity and larger absolute increases in CK activity levels when supplementing with tart cherry juice compared to placebo up to 48-h of recovery despite never reaching statistical significance (9). In lieu of these results, Bowtell et al. (20) also demonstrated a trend for a smaller percent change from pre-exercise levels in post-exercise CK levels up to 48-h of exercise recovery. Unfortunately, with no other tart cherry supplement study as a basis for comparison when utilizing a resistance-based exercise modality, the results presented demonstrates conflicting, non-significant evidence that needs additional research support. A smaller percentage change from pre-exercise levels in the tart cherry supplemented group compared to placebo may begin to establish evidence for potential post-exercise secondary muscle damage attenuation, but can only be speculative at this point.

Inflammatory and Anti-Inflammatory Response to Endurance Exercise

Previous research in the literature seems to conclude that the inflammatory process is mediated by both pro-inflammatory cytokines (63) and neuroendocrinological

factors (138). However, it has also been demonstrated that as major players in the development of secondary muscle damage, neutrophils, may also amplify the release of inflammatory cytokines (26, 172).

Effects of NSAIDs

Recruiting trained male and female ultramarathon runners competing in the 160 km Western States Endurance Run event, Nieman et al. (130) categorized athletes as NSAID users and non-users based on self-reported NSAID utilization during the race. The overwhelming majority of NSAID users supplemented with ibuprofen. As a result of the ultramarathon event, Nieman et al. (130) described significant increases over pre-run levels in all seven cytokines measured: IL-6 (125-fold increase over pre-race), IL-10 (24-fold), granulocyte colony-stimulating factor (G-CSF) (12-fold), IL-8 (5-fold), monocyte chemotactic protein 1 (MCP-1) (3-fold), and macrophage inflammatory protein 1β (MIP-1β) (1.2-fold). More importantly, Nieman et al. (130) reported greater post-run increases in markers of IL-6, IL-8, G-CSF, MCP-1, and MIP-1β for those self-described as NSAID users versus those who refrained from NSAID use during the ultramarathon event. As an important notation, Nieman et al. (130) determined from statistical analysis that self-selected supplementation with antioxidants either in the months before or during the race had no effect on DOMS, serum CPK, or changes in cytokines.

Although there is only one study that has analyzed the inflammatory response to a single bout of endurance exercise with NSAID supplementation, the results seems consistent across several markers. However, this particular study was not designed as a

supplement intervention study and relied on subject self-reporting to determine criteria for NSAID intake over the course of the ultramarathon race. With less structure, this self-reported study design allows for greater variability in supplementation type, dose, and frequency. However, the smaller amount of structure also provides for a more realistic, free living snap shot of NSAID supplement effects rather than a more controlled study design that may not be as applicable. Based on the results of this study, it seems as though supplementation with NSAIDs (primarily ibuprofen) over the course of an ultra-distance endurance race contributes to greater release of inflammatory markers into the plasma compared to those who refrained from NSAID usage.

Effects of Antioxidant Vitamins

In an endurance-based cycling study recruiting healthy, moderately trained males, Davison and Gleeson (133) supplemented subjects with four different interventions before and during the exercise bout: placebo, carbohydrate (6% w/v or approximately 137 g CHO) only beverage, vitamin C (0.15% w/v or approximately 3400 mg) only beverage, or a combination beverage consisting of carbohydrate + vitamin C. The endurance exercise challenge completed by subjects within the study was a 2.5-h cycling bout at 60% VO_2 max. Post-exercise plasma IL-6 concentrations was not affected by vitamin C supplementation alone, but when combined with a carbohydrate source, post-exercise IL-6 levels tended to be lower compared to placebo (133). In a second study conducted by Davison and Gleeson (165) the following year employing well-trained cyclists and the same endurance cycling bout described in the previously study, subjects were supplemented vitamin C (1000 mg/d) or a placebo for 14-d. Similar

to the first study in the healthy, active males, there was no significant effect of supplementation reported by Davison and Gleeson (165) on plasma IL-6 concentrations following the 2.5-h cycling bout despite an IL-6 increase immediately and 1-h post-exercise. Similar to the first study cohort and endurance exercise protocol utilized by Davison and Gleeson (133), Hagobian et al. (70) studied the effects of supplementing recreationally trained men with an antioxidant cocktail for 3-wk prior to an 3-h high-altitude (4300 m elevation) cycling bout at 55% VO_2 max. In this placebo-controlled study, participants were supplemented with either the antioxidant supplement (10,000 IU β-carotene, 200 IU α-tocopherol acetate, 250 mg ascorbic acid, 50 μg selenium, 15 mg zinc) or a placebo twice per day for 3-wk. Blood samples were taken at rest, immediately, 2, 4, and 20-h post-exercise. Hagobian et al. (70) reported plasma IL-6 elevations at all post-exercise time points compared to pre-exercise values and elevated plasma CRP levels at 20-h post-exercise with no effect of supplementation on either response. Further, Hagobian et al. (70) described a plasma TNF-α concentration that remained unaffected by the exercise bout or supplementation.

In a shorter endurance-cycling based study in healthy, non-athlete volunteers, Vassilakopoulos et al. (105) supplemented subjects with an antioxidant combination (60-d of vitamins A, C, and E; 15-d of allopurinol; and 3-d of *N*-acetylcysteine) prior to a 45-min bout of cycling at 70% VO_2 max. Blood samples were drawn at baseline, immediately, 30-min, and 120-min post-exercise. As a result of the antioxidant cocktail, plasma post-exercise concentrations of IL-1β, TNF-α, and IL-6 were significantly attenuated compared to post-exercise levels prior to supplementation. Further, the

pharmacokinetic response as measured by area under the curve (AUC) for IL-1β, TNF-α, and IL-6 were all significantly smaller than the AUC values calculated following exercise prior to supplementation.

Peterson et al. (140) in a placebo-controlled study, supplemented male recreationally-trained runners with either an vitamin C (500 mg/d) + vitamin E (400 mg/d) combination or a placebo for 14-d before and 7-d after a 90-min treadmill run at a 5% decline and 75% VO_2 max. Despite a 20-fold increase in plasma IL-6 and 3-fold increase in plasma IL-1ra post-exercise, Peterson et al. (140), described no effect of the antioxidant vitamin combination on plasma anti-inflammatory cytokines. Thompson et al. (184) supplemented subjects with vitamin C or placebo for 14-d surrounding a prolonged 90-min high-intensity intermittent shuttle running test (LIST). Subjects were supplemented twice daily (morning and evening) with vitamin C (400 mg/d) or a placebo. As a result of the differences in supplementation, Thompson et al. (184) demonstrated that serum IL-6 concentrations increased 8-fold immediately post-exercise, but returned to baseline levels by 24-h post-exercise in both groups. IL-6 concentrations in the vitamin C group began to decrease 1-h post-exercise compared to a continued IL-6 increase in the placebo group so much so that vitamin C group levels were significantly lower than placebo 2-h post-exercise. In response to the LIST exercise challenge, Thompson et al. (184) also published that the serum CRP response was not different between groups, but increased 2-fold over pre-exercise values 24-h post-exercise and remained elevated through 48-h of recovery.

Over the course of the studies listed in this section, there is a lack of congruent evidence with respect to the effectiveness of antioxidant vitamins or antioxidant vitamin combinations on markers inflammation. With a direct effect on redox balance within the muscle cell environment, the magnitude of inflammation could have been affected if the absorption pharmacokinetics of these supplements were greater than the placebo. Many of the studies listed in this section tested for the same serum markers of inflammation, but provided inconsistent results. The inconsistency may be due to the large variation in type of supplement, exercise modality, duration of exercise, duration and quantity of supplementation, study population (trained versus untrained), previous dietary antioxidant status, and endogenous antioxidant status.

Effects of Phytochemicals and Functional Foods

A study by Nieman et al. (131) supplemented trained cyclists with 400 mg of quercetin, quercetin-EGCG (epigallocatechin 3-gallate), or placebo soft chews for 24-d surrounding 3-d of consecutive bouts of 3-h submaximal cycling. Nieman et al. (131) reported a significant decreases in plasma concentrations of both inflammatory and anti-inflammatory markers (CRP, IL-6, and IL-10) immediately post-exercise on the third consecutive exercise day in the quercetin-EGCG group compared to placebo. An acute supplementation study providing moderately active subjects with 48 g of anthocyanin-rich black currant extract immediately surrounding a single bout of high-intensity rowing conducted by Lyall et al. (109) demonstrated a significant post-exercise attenuation of pro-inflammatory cytokine production from LPS-stimulated cells following extract supplementation compared to placebo. Lyall et al. (109) postulated from subsequent in

vitro experimentation that this reduced cytokine production may have resulted from anthocyanin-based inhibition of NF-κB-mediated mechanisms. Lafay et al. (102) employed a crossover design study with a variety of elite male sportsman to investigate the effects of a polyphenol-rich grape extract (400 mg/d) compared to placebo (400 mg/d) supplementation over a 30-d training and competition period. As inflammatory biomarker, Lafay et al. (102) reported a significant increase in urinary excretion of isoprostanes with placebo supplementation compared to no change from baseline values with grape extract ingestion. Supplementing highly trained male rowers of the Polish national team with plant superoxide dismutase extract (GliSODin) daily (500 mg/d) for 6-wk, Skarpanska-Stejnborn et al. (170) required subjects to perform a 2,000 m maximum-effort test on a rowing ergometer with blood samples drawn pre-exercise, 1-min, and 24-hr post-exercise. Skarpanska-Stejnborn et al. (170) demonstrated that CRP levels were significantly lower in the GliSODin group compared to placebo pre-exercise, immediately post-exercise, and 24-h of recovery.

Subjects across all four of these studies were supplemented with very different phytochemical and functional food supplements surrounding bouts of varying endurance exercise. However, the results from all four of these studies agree that supplementation with natural phytochemicals derived from food-based sources likely to contain large amounts of polyphenols and anthocyanins is effective in attenuating inflammation within the muscular environment in response to exercise-induced muscle damage. Mechanistically, the attenuated muscle damage markers are a result of better redox

balance and decreased impetus of perceived stress within the sarcoplasmic and myocellular environment.

Effects of Tart Cherry Supplementation

In an aerobic-based crossover study, Ducharme et al. (50) performed a standard stepwise treadmill running protocol on a small cohort of healthy, but untrained horses that were administered either a tart cherry juice blend or placebo for 14-d prior to the exercise. Ducharme et al. (50) analyzed serum amyloid A (SAA) as a marker of inflammation and reported a significant increase in SAA concentration in response to the incremental exercise protocol with no significant differences between treatments. In a study examining the effects of supplementation on endurance-trained humans, Howatson et al. (76) reported significantly lower markers of inflammation (IL-6 and C-reactive protein (CRP)) after running a marathon that coincided with quicker recovery of knee extensor maximal strength following the marathon in Montmorency tart cherry juice supplemented subjects compared to placebo. IL-6 markers where significantly attenuated immediately post-race, whereas CRP levels were significantly lower 24-h and 48-h post-run with tart cherry consumption compared to placebo (9, 76). Dimitriou et al. (47) also recently conducted a marathon-based study on recreationally trained marathon runners and supplemented subjects with either a Montmorency cherry juice blend or placebo for 8-d (5-d pre-race, day of race, and 2-d post-race) surrounding the marathon race. Similar marathon-based study conducted by Howatson et al. (76), Dimitriou et al. (47) also reported significantly lower CRP levels 24-h and 48-h post-run with blended tart cherry juice consumption versus placebo. In support of these two marathon-based

studies, Kelley et al. (93) demonstrated decreases in circulating hsCRP in healthy volunteers following 4-wk of Bing sweet cherry supplementation, helping to further elucidate the anti-inflammatory benefits of anthocyanins (9).

As seen in the previous section with the phytochemicals and functional foods, tart cherry juice supplementation in humans following bouts of endurance challenges, specifically a marathon, researchers commonly reported decreased markers of inflammation compared to those supplementing with a placebo. Despite supplementing race horses with a similar tart cherry juice, Ducharme et al. (50) only measured SAA as a marker of inflammation, leaving no basis of comparison to the other endurance-based studies. Further, the small cohort of racehorse subjects by Ducharme et al. (50) could have also been a confounding factor.

Inflammatory and Anti-Inflammatory Response to Resistance-Based Exercise

Effects of Antioxidant Vitamins

In a resistance exercise-based, placebo-controlled study, Fischer et al. (57) supplemented a cohort of physically active males with a combination of vitamin C (500 mg/d) and *RRR*-α-tocopherol (400 IU/day) 4-wk prior to and 1-d after a resistance exercise challenge. As part of the study protocol, subjects performed 3-h of two-legged dynamic knee-extensor exercise at 60 leg extensions per minute at 50% their maximum power output. Blood samples were obtained from the femoral vein at rest (0-h), during exercise (0.5, 1, 2, and 3-h), and during post-exercise recovery (3.5, 4, 5, and 6-h) with the last study blood sample obtained from an antecubital vein and 23-h post-exercise. As a result of plasma IL-6, IL-1 receptor agonist (IL-1ra), and CRP analysis, Fischer et

al. (57) reported a post-exercise attenuation in plasma inflammatory marker concentration as a result of the antioxidant combination supplementation compared to placebo. In an upper body-based resistance exercise bout, Childs et al. (32) supplemented previously untrained subjects with either a placebo or a vitamin C (12.5 mg/kg body weight) + N-acetyl-cysteine (NAC) (10 mg/kg body weight) combination for 7-d after a resistance exercise challenge. Within the exercise protocol, subjects were asked to perform 3 sets of 10 repetitions of eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. As a result of the eccentric-exercise bout, IL-6 levels were significantly elevated over pre-exercise levels at 48-h post-exercise with no treatment effect. However, Childs et al. (32) measured myeloperoxidase (MPO) as a secondary mechanism to quantify the severity of inflammation. Similar to the IL-6 response, MPO was significantly elevated 48-h post-exercise in both supplementation groups, but those supplementing with the vitamin C + NAC combination demonstrated a 33% attenuation compared to placebo at that same time point.

The quantity of muscular involvement and volume of exercise between the two studies was greatly different as Fischer et al. (57) asked subjects to perform an eccentrically resisted double leg extension for 3-h compared to Childs et al. (32) only requiring subjects to perform 3 sets of 10 eccentrically-resisted arm curls. Both studies produced some type of inflammatory response as indicated by the significant increase in IL-6 levels over baseline values. Additionally, Childs et al. (32) only supplemented subjects following the eccentric exercise bout, which may explain only the partial effectiveness of antioxidant vitamin supplementation on attenuation of post-exercise

markers of inflammation compared to a placebo. Overall, both studies indicate that there may be some promise with acute antioxidant vitamin supplementation on attenuation of post-resistance exercise inflammatory markers.

Effects of Phytochemicals and Functional Foods

Utilizing a crossover study design, Trombold et al. (189) recruited recreationally active males to supplement twice daily with either a pomegranate juice (960 mL/d) or a placebo (960 mL/d) over a 9-d period (4-d pre-exercise, day of, and 4-d post-exercise) surrounding a single workout involving two sets of 20 maximal eccentrically-resisted elbow flexions. Trombold et al. (189) tested IL-6 and CRP as serum markers of inflammation surrounding the exercise bout and found no significant alterations over time or between groups for either maker as a result of the eccentric exercise. In an earlier study examining the effects of eccentrically-resisted elbow flexions, Phillips et al. (142) treated untrained subjects with either a placebo or mixed functional food-derived antioxidant supplement for 14-d (7-d pre-exercise and 7-d post-exercise). The mixed functional food supplement consisted of mixed tocopherols (300 mg/d), DHA, (800 mg/d), and flavonoids (100 mg/d hesperetin and 200 mg/d quercetin). Nearly identical to the exercise protocol used by Childs et al. (32), subjects were asked to perform 3 sets of 10 repetitions of eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. Phillips et al. (142) published that subjects ingesting the functional-food antioxidant combination for 14-d (7-d pre-exercise and 7-d post-exercise) surrounding a bout of eccentrically-resisted arm curls, had a smaller elevation from pre-exercise levels of IL-6 3-d post-exercise compared to placebo. Phillips et al. (142) also

found that supplementation with the functional food antioxidant combination correlated to a significant attenuation in CRP elevation from baseline levels 72-h post-exercise compared to placebo. Examining intramuscular adaptations to a single bout of eccentrically-resisted isokinetic leg extensions on the dominant leg, Kerksick et al. (94) supplemented active males for 14-d with either *N*-acetyl-cysteine (NAC) (1,800 mg/d), epigallocatechin gallate (EGCG) (1,800 mg/d), or a placebo. Assessment of inflammation as a result of the eccentric-exercise bout, Kerksick et al. (94) demonstrated no supplementation effect on TNF-α or the neutrophil:lymphocyte ratio. Over time, whole blood neutrophil:lymphocyte levels peaked 6-h post-exercise and remained elevated above baseline over the course of the entire 72-h recovery (94). No changes over time were reported for TNF-α.

The evidence across these three resistance-based, functional food supplement studies seems to be equivocal. The two studies conducted with recreationally trained or active subjects did not find any significant effects of supplementation on markers of inflammation compared to the study conducted by Phillips et al. (142) on untrained subjects. However, the comprehensive phytochemical supplementation concoction utilized by Phillips et al. (142) may have been simply more effective than the supplements utilized in the other two studies. Within this research grouping, the lower body resistance-based study conducted by Kerksick et al. (94) did not follow the pattern of the previous antioxidant vitamin studies as this research group did not find any significant differences in inflammatory markers across the treatment groups. However, the markers of inflammation analyzed in this study were not comparable to the other two

conducted with similar supplementation, making the comparison difficult. In the end, current inflammatory research among resistance-based studies implementing functional food and phytochemical supplementation remains inconclusive.

Effects of Tart Cherry Supplementation

Acute, intensive resistance exercise (> 60% 1-RM) has been reported to significantly increase muscular mechanical trauma as the initial phase of injury (20, 78). In a strength-based supplement study with resistance trained subjects, Bowtell et al. (20) was not able to detect any significant effects on markers of inflammation (IL-6 and hsCRP). However, this study did report a trend for greater hsCRP levels in the placebo group following the bout of eccentric leg extensions compared to Montmorency cherry juice concentrate supplementation (9, 20).

With no basis of study comparison, even with the three studies utilizing other phytochemical and functional food supplements, it is difficult to align the inconclusive results of this study as the aforementioned lower body resistance-based study conducted by Kerksick et al. (94) did not measure CRP levels and the two previously mentioned upper body resistance-based studies found conflicting evidence. Unfortunately, the trend for attenuated hsCRP levels coupled with no significant effects on IL-6 reported by Bowtell et al. (20) provides less clarification on tart cherry, anthocyanin, and polyphenol supplementation effects on post-exercise markers of inflammation following bouts of resistance-based exercise.

Hormonal Physiological Stress in Response to Exercise

The increase in inflammatory-related cytokines and chemokines such as TNF-α, IL-1β, IL-6, and IL-8 during and immediately following exercise has been shown in previous research (63, 134, 138) and closely resembles the inflammatory response in the current study. As described in previous research, the increase in serum IL-6 within both groups 60-min post-lift in the current study can likely be attributed to the large release of muscle-derived IL-6 as a result of the contracting muscle fibers (63, 175). The influx of muscle-derived IL-6 within the systemic circulation may be one of the triggers for subsequent cortisol release in response to exercise-induced stress (63, 174). Glucocorticoids, specifically cortisol, and anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 are released during strenuous exercise and typically demonstrate an immunosuppressive influence to help modulate the immune response balance (64). However, extended immunodepression due to elevated plasma cortisol during the post-exercise period, particularly following long bouts of intense training in the fasted state (63), may hinder recovery and subsequent performance. Glucocorticoids, specifically cortisol, released due to activation of the stress response through muscle mechanical microtrauma and ROS production have demonstrated an immunosuppressive influence.

Effects of Antioxidant Vitamins

Previous research conducted by McAnulty et al. (116) in trained endurance athletes reported a significant cortisol increase over time, but no significant difference in immediate and 1.5-h post-race cortisol levels with 2-month vitamin E supplementation compared to placebo. Davison and Gleeson (133), in an investigation of moderately

trained males during 2.5-h moderate intensity cycling compared the effects of a beverage containing a vitamin C supplement with and without carbohydrate before and during endurance exercise. This study revealed a significant increase in plasma cortisol levels immediately and 1-h post-exercise in both the placebo and vitamin C only supplemented groups with no significant difference between these two groups at 1-h post-exercise (133). The addition of carbohydrates (alone or with vitamin C) significantly lowered the cortisol response during the exercise recovery up to 1-h post-exercise (133). This result demonstrates a potentially lower physiological stress in the short-term post-exercise period due to a higher energy state. In the second study conducted by Davison and Gleeson (165) the following year employing well-trained cyclists to complete a 2.5-h endurance cycling bout at 60% VO_2 max, subjects were supplemented vitamin C (1000 mg/d) or a placebo for 14-d. Contrary to the results of the previous study using healthy, active males, Davison and Gleeson (165) determined that there was a tendency for supplementation to have an effect on plasma cortisol levels immediately and 1-h following the 2.5-h cycling bout. In an endurance running-based study, Thompson et al. (184) supplemented subjects with vitamin C or placebo for 14-d surrounding a prolonged 90-min high-intensity intermittent shuttle running test (LIST). Subjects were supplemented twice daily (morning and evening) with vitamin C (400 mg/d) or a placebo. As a result of the LIST exercise challenge, Thompson et al. (184) demonstrated an increase in serum cortisol levels above pre-exercise values immediately and 1-h post-exercise in both treatment groups, with a tendency for serum cortisol to be lower in the vitamin C group versus placebo.

In a placebo-controlled study, Fischer et al. (57) supplemented a cohort of physically active males with a combination of vitamin C (500 mg/d) and *RRR*-α-tocopherol (400 IU/day) 4-wk prior to and 1-d after a resistance exercise challenge. Subjects performed 3-h of two-legged dynamic knee-extensor exercise at 60 leg extensions per minute at 50% their maximum power output. Fischer et al. (57) reported a post-exercise increase in plasma cortisol levels from 0-h to 6-h of recovery, compared to a blunted plasma cortisol response during the same time period in subjects ingesting the antioxidant vitamin combination.

Although not with full certainly from all studies listed, a trend that seems to be developing toward beneficial effects of vitamin C or an antioxidant combination incorporating vitamin C on the reduction of post-exercise serum cortisol levels following both endurance and resistance exercise bouts. The supplementation protocol utilized in the study conducted by Davison and Gleeson (133) may have produced varying results dependent on carbohydrate incorporation to help lower the physiological perception of stress due to the beverage formulation of the supplement. The beverage containing vitamin C compared to a vitamin C supplement may have altered the absorption kinetics enough to alter the effectiveness of the antioxidant supplement. Further, both studies that reported no significant differences in post-exercise cortisol levels among the treatment groups employed trained athletes as subjects. The training status of the subject cohort could have certainly altered the research outcome compared to research using untrained or only recreationally trained individuals due to the differences in overall physiological adaptations to exercise-related stress.

Effects of Phytochemicals and Functional Foods

Comparing 14-d supplementation of *N*-acetyl-cysteine (NAC), epigallocatechin gallate (EGCG), or a placebo in active males surrounding a single bout of eccentric knee-extensor exercise, Kerksick et al. (94) found a significant decrease in serum cortisol levels 6-h post-exercise, but no differences between groups up to 72-h post-exercise despite a significant blunting of muscle soreness perception 24-h post exercise in the two supplement groups compared to placebo. The current study demonstrated an increase in cortisol levels 60-min post-lift compared to pre-lift in both groups.

The results of this particular study do not align with those reported by the other resistance-based exercise and antioxidant supplementation study Fischer et al. (57) published. However, the extremely high volume of the study conducted by Fischer et al. (57) may be better classified as a muscular endurance study rather than resistance-based. The aforementioned findings published by Kerksick et al. (94) allude to the fact that either the NAC or EGCG supplement mechanism of action to aid in blunting muscle soreness is disconnected from physiological perceptions of stress. With limited research previously conducted in this category, future investigations are necessary to solidify potential mechanisms.

Effects of Tart Cherry Supplementation

Dimitriou et al. (47) in the marathon-based study on recreationally trained marathon runners is the only tart cherry supplementation-based study that measured a cortisol response. Despite an elevated salivary cortisol level immediately post-race compared to pre-race levels, Dimitriou et al. (47) reported that these levels returned to

pre-race values within 24-h post-marathon with no difference in salivary cortisol across treatment groups up to 48-h of marathon recovery.

Similar to the findings described by Kerksick et al. (94), the salivary cortisol findings of this particular endurance-based exercise study did not find any significant effect with tart cherry supplementation compared to placebo. This is the only study that examined exercise and tart cherry supplementation with any type of hormonal catabolic or anabolic marker, providing no basis for comparison. Further, nearly all of the previous research mentioned used serum or plasma cortisol tests to determine changes, also leaving this study employing salivary cortisol measurement difficult to compare to others. Once again, further research is necessary to solidify results and elucidate potential mechanisms.

Antioxidant and Antiradical Activity Response to Exercise

Within the literature, there are multiple methodologies employed to analyze antioxidant and antiradical activity. Oxygen radical absorbance capacity (ORAC) can be measured in plasma samples and is widely used in biological sample analysis of antioxidant capacity (102). The ORAC method is based on the thermal-decomposition of azo compounds that inhibits peroxy-radical-induced oxidation (28, 102). Ferric reducing ability of plasma (FRAP) can also be employed to analyze antioxidant capacity. This particular technique is based upon the fact that water soluble reducing agents or antioxidants in the blood plasma will act to reduce ferric ions to ferrous ions, preparing the ions for reaction with chromogen as a detecting agent (115).

Effects of NSAIDs

McAnulty et al. (115) recruited a large cohort of runners competing in the 160 km Western States Endurance Run event to study the effects of NSAID supplementation and categorized them based on their self-selected NSAID use over the course of the race. McAnulty et al. (115) employed the FRAP method to detect changes in plasma antioxidant potential and determined that despite a significant post-race FRAP elevation, there were no detectable differences between the NSAID users and non-users over the course of the 7-d recovery.

While this particular stands by itself within the literature with respect to self-reported NSAID supplementation surrounding an ultra-endurance event, NSAID supplementation did not seem to have an effect on systemic reducing or antioxidant capacities within the plasma over the course of the 7-d recovery period. Utilizing the FRAP method to analyze changes in plasma antioxidant potential does make it difficult to compare to other endurance and resistance-based studies due to the low number of studies employing that methodology. Further research and studies need to be conducted in this area to confirm these results.

Effects of Antioxidant Vitamins

Childs et al. (32) analyzing TAS following arm eccentric exercise-induced injury also demonstrated significantly greater TAS levels with vitamin C + NAC supplementation compared to placebo 48-h through 7-d post-exercise recovery in healthy, untrained males. Comparatively, the placebo group did not show any significant change from baseline line plasma TAS activity in the 7-d following the

eccentric-exercise challenge. Davison and Gleeson (133), in an investigation of healthy and active males during 2.5-h moderate intensity cycling compared the effects of a beverage containing a vitamin C supplement with and without carbohydrate before and during endurance exercise. As a result of acute beverage ingestion, plasma antioxidant capacity (PAC) levels were significantly elevated above placebo immediately post-exercise when supplemented with vitamin C only and 1-h post-exercise when supplemented with the CHO + vitamin C combination. In the second study conducted by Davison and Gleeson (165) the following year using well-trained cyclists to complete a 2.5-h endurance cycling bout at 60% VO_2 max, subjects were supplemented vitamin C (1000 mg/d) or a placebo for 14-d. Unlike the results of the previous study, Davison and Gleeson (165) demonstrated changes in PAC over the study time period, but no effect of vitamin C supplementation following endurance exercise compared to placebo.

Based on comparing the results of these three studies, it seems at first glance that all of the vitamin C based supplements had a positive effect on antioxidant status in the untrained populations, but no effect compared to placebo in the trained population. This conclusion is perhaps most evident in the two cycling-based endurance studies conducted by Davison and Gleeson (133, 165) where the same duration of exercise was utilized with similar comparable supplements in both the trained and untrained populations. Further, the supplementation period was very different across these studies as one employed more of an acute supplementation timeline and other was conducted over 14-d prior to the endurance exercise bout. Due to the differences in study design, subject population, and time course of supplementation, it is difficult to formulate a

definitive conclusion with antioxidant vitamin supplementation on overall changes in antioxidant capacity during exercise recovery.

Effects of Phytochemicals and Functional Foods

Interestingly, in a crossover design study conducted in trained cyclists by Morillas-Ruiz et al. (125), subjects performed a 90-min submaximal endurance time trial at 70% VO_2 max on a cycle ergometer while consuming a commercial antioxidant beverage containing fruit concentrates (black grape, raspberry, and red currant) and carbohydrates at 15-min intervals over the course of the entire testing protocol for a total juice consumption of 1600 ml. Assessing plasmatic antioxidant activity, Morillas-Ruiz et al. (125) found no difference in TAS immediately and 45-min post-exercise between antioxidant beverage and placebo groups despite levels lower than the typical adult population (125). Evaluating a wide variety of male sportsman during their training and competitive seasons, Lafay et al. (102) employed a crossover study design to investigate the effects of a polyphenol-rich grape extract (400 mg/d) compared to placebo (400 mg/d) supplementation over a 30-d period. Lafay et al. (102) used two different methods to determine changes in plasma antioxidant capacity: 1) ORAC and 2) FRAP. Both analysis methods conferred on an increase in plasma antioxidant capacity with grape extract consumption compared to placebo. Specifically, grape extract consumption via the ORAC analysis method increased plasma antioxidant capacity after 30-d of supplementation versus the placebo levels that remained unchanged over the same period (102). Utilizing the FRAP method, plasma antioxidant capacity

significantly decreased with placebo supplementation, while levels were maintained within the grape extract group (102).

In the first placebo-controlled study utilizing a cohort of highly trained male rowers of the Polish national team, Skarpanska-Stejnborn et al. (169) supplemented athletes with artichoke-leaf extract (1,200 mg/d) or a placebo 3 times per day for 5-wk. Skarpanska-Stejnborn et al. (169) required subjects to perform a 2,000 m maximum-effort test on a rowing ergometer as the exercise performance intervention with blood samples drawn pre-exercise, 1-min, and 24-hr post-exercise. As a result of the supplementation, plasma TAC was significantly higher in the artichoke-leaf extract group before, immediately post, and 24-h post-maximal rowing exercise. In the second study using this rowing athlete population, Skarpanska-Stejnborn et al. (168) supplemented subjects with *Rhodiola* rosea extract (200 mg/d) or a placebo 2 times per day for 4-wk. This study reported the same TAC results as those demonstrated with artichoke-leaf extract supplementation. Supplementing highly trained male rowers of the Polish national team with plant-based superoxide dismutase extract (GliSODin) daily (500 mg/d) for 6-wk in their most recent study, Skarpanska-Stejnborn et al. (170) required subjects to perform the same 2,000 m maximum-effort test on a rowing ergometer. TAC levels increased significantly over pre-exercise levels immediately post-exercise and returned to pre-exercise levels 24-h post-exercise in both groups.

Within the endurance studies listed in this particular section, the various polyphenol-based supplements utilized seem to have been effective in maintaining an increased level of antioxidant capacity over the course of the recovery period. The

superoxide dismutase extract derived from a plant source implemented in the third of three studies conducted on rowers from the Polish national team by Skarpanska-Stejnborn et al. (170) did not have any effect on antioxidant status compared to the placebo and the other two polyphenol-derived supplements used in the previous two studies. In this grouping of studies, the training status of the subjects did not seem to be a major factor in the study outcome. The endurance-based study conducted in trained cyclists by Morillas-Ruiz et al. (125) did not report any differences between the antioxidant beverage supplement and a placebo due likely to the short time duration of the ingestion only over the course of the 90-min study protocol. This short duration of ingestion may have limited the effectiveness of the supplement with respect to improving antioxidant capacity.

Effects of Tart Cherry Supplementation

The increase in antioxidant bioavailability from acute tart cherry supplementation containing high levels of flavonoids and anthocyanins (166, 199) has been hypothesized to be one of the primary benefits in support of endogenous antioxidant systems following strenuous exercise and excessive ROS-production. Howatson et al. (84) analyzed plasma TAS, as a measure of antioxidant or antiradical activity across all biological components, following a full marathon in trained endurance runners, and found that TAS was significantly greater in the tart cherry supplemented group compared to control across all time points (pre-race and up to 48-h post-race) (9, 76, 172). Unlike the tart cherry group, the placebo group fell below baseline values 48-h post-run, thus failing to maintain TAS or redox balance following the endurance

exercise. This demonstrates possible tart cherry antioxidant effectiveness on excessive ROS production with bouts of endurance exercise (9).

The effectiveness of the tart cherry supplement within this study surrounding a full marathon run in trained endurance runners appears to closely align with the results found in the previous studies listed in the phytochemical and functional food section. The increase in antioxidant and antiradical activity as a result of tart cherry supplementation may be due to the anthocyanin effects on iNOS gene expression and subsequent attenuation of nitric oxide production helping the system maintain a more balanced redox status compared to runners supplemented with the placebo. Additional studies in the future utilizing a similar protocol, supplement, and study cohort would help solidify these initial mechanistic speculations.

Free Radical and Oxidative Stress Response to Endurance Exercise

Evidence in the literature utilizing lipid peroxidation (TBARS assays) analysis has presented a potential lack of oxidative damage detection specificity in human studies that may also explain the variability in results among previous studies (9, 12, 13, 193). Similarly, measurement of protein carbonyls (PC) as a marker of protein oxidation and overall oxidative stress surrounding bouts of exercise has sparked controversy in the literature due to the lack of reliability and specificity of the marker to discriminate between sources of oxidative damage (9, 193).

Effects of NSAIDs

Before the 160 km Western States Endurance Run event, McAnulty et al. (115) recruited a large cohort of runners competing in the race to study the effects of NSAID

supplementation on muscle injury and oxidative stress. As a result, the researchers categorized the runners based on their self-selected NSAID use over the course of the race. Measuring differences in oxidative stress as a result of the endurance race, McAnulty et al. (115) observed changes in plasma F_2-isoprostanes, lipid hydroxides (LOOH), and protein carbonyls (PC). The endurance run caused significant increases in plasma F_2-isoprostane levels when both groups were combined, but there were not any significant changes between groups as a result of supplementation differences. Both the endurance event and NSAID ingestion status had no effect on LOOH levels over the course of the study protocol. PC plasma concentrations, a marker of protein oxidation, were significantly increased over pre-exercise levels in the NSAID user group with the response being significantly greater than non-NSAID users (115).

Despite an increase in markers of protein oxidation in NSAID self-reported users, McAnulty et al. (115) did not report any significant differences between NSAID users and non-users with respect to serum markers of muscle damage and catabolism. The increase in plasma PC concentrations does not align with the results of the other two free radical and oxidative stress markers measured. Additional research needs to be conducted in the future to confirm these protein oxidative results when supplementing with NSAIDs during and post-ultra-endurance exercise as PC assay results can be highly variable.

Effects of Antioxidant Vitamins

As a highly reactive oxide metabolite of nitric oxide, peroxynitrate-bound tyrosine residues forming nitrotyrosine (NT) (196) was measured by Sureda et al. (178)

following supplementation of vitamin C + vitamin E surrounding a half-marathon. Suerda et al. (178) reported a significant increase in NT immediately post-race and 3-h post-race in the placebo group compared to the vitamin C + vitamin E supplemented group, indicating that antioxidant supplementation may have a dampening effect on oxidation of nitrogen-containing compounds with endurance exercise. Attempting to simulate multi-sprint sports, Thompson et al. (183) recruited habitually active males within a crossover design study to ingest a vitamin C supplement (1 g dose) or a placebo 2-h prior to a 90-min intermittent shuttle-running test. In measuring MDA as a marker of oxidative stress, Thompson et al. (183) reported that plasma MDA concentrations significantly increased over baseline values immediately post-LIST exercise, but then returned to baseline levels up to 72-h post-LIST with no differences described between supplementation trials. In another placebo-controlled, running-based study conducted by Thompson et al. (184) within the same year in physically active males, supplementation of vitamin C or placebo was carried out for 14-d surrounding a prolonged 90-min high-intensity intermittent shuttle running test (LIST). Subjects were supplemented twice daily (morning and evening) with vitamin C (400 mg/d) or a placebo. Within this particular study, Thompson et al. (184) reported an increase in plasma MDA concentrations, with no statistical differences reported between treatments. However, Thompson et al. (184) stated that plasma MDA concentrations at 24-h post-LIST exercise were significantly greater than pre-exercise levels in the placebo group versus MDA concentrations in the vitamin C group that were not different than baseline levels. Further, Thompson et al. (184) described an increase post-exercise in serum uric acid

concentrations that remained above baseline levels at 24-h of recovery with no effect of treatment.

In an investigation conducted by Davison and Gleeson (165) recruiting well-trained cyclists to complete a 2.5-h endurance cycling bout at 60% VO_2 max, subjects were supplemented vitamin C (1000 mg/d) or a placebo for 14-d. Contrary to the results published by Thompson et al. (183), Davison and Gleeson (165) reported that plasma MDA levels were unaffected by the cycling exercise bout and vitamin C supplementation had no effect on MDA immediately and 1-h following the 2.5-h cycling bout.

The only study that reported differing results supplemented trained runners with a vitamin C + E combination that may have been more effective than the other three studies conducted using endurance-based exercise and vitamin C supplementation. However, in this particular study, Sureda et al. (178) only measured NT as a marker of nitric oxide metabolism compared to the other three studies that utilized MDA as a marker of oxidative stress. Both the differences in antioxidant vitamin supplement and marker to measure oxidative stress may have contributed to the differences in results across the four studies listed in this section.

Effects of Phytochemicals and Functional Foods

In an endurance-based study, Pilaczynska-Szczesniak et al. (144) recruited male members of the Polish rowing team to ingest 50 mL of chokeberry juice or placebo three times daily (150 mL/d) over the course of their 4-wk training camp. At the beginning and end of the training camp, the crew athletes performed a 2000-m rowing test followed

by an incremental rowing session after a 1-d rest. At the end of the 4-wk training camp and supplementation period, Pilaczynska-Szczesniak et al. (144) reported that serum TBARS levels were significantly attenuated in the chokeberry supplemented group compared to placebo at 1-min and 24-h post-incremental rowing test. Additionally, subjects supplementing with chokeberry juice demonstrated lower glutathione peroxidase (GPx) activity 1-min post-incremental test and lower SOD activity 24-h post incremental test compared to placebo (144). Utilizing a similar cohort of highly trained male rowers of the Polish national team, Skarpanska-Stejnborn et al. (169) supplemented athletes with artichoke-leaf extract (1,200 mg/d) or a placebo 3 times per day for 5-wk. Skarpanska-Stejnborn et al. (169) required subjects to perform a 2,000 m maximum-effort test on a rowing ergometer as the exercise performance intervention with blood samples drawn pre-exercise, 1-min, and 24-hr post-exercise. While there was no significant differences reported in SOD activity between the groups as a result of supplementation, Skarpanska-Stejnborn et al. (169) described a tendency for a decrease in SOD activity with artichoke-extract supplementation compared to an increasing SOD activity trend in the placebo group. Despite no significant group interaction with respect to TBARS levels, Skarpanska-Stejnborn et al. (169) reported a greater increase in TBARS levels above pre-exercise values immediately after the rowing exercise in the placebo group compared to artichoke-extract (35% vs. 12%). Further, TBARS concentrations returned pre-exercise levels 24-h post-exercise in the artichoke group, while TBARS remained elevated during recovery in the placebo group.

In the second study using this rowing athlete population, Skarpanska-Stejnborn et al. (168) supplemented subjects with *Rhodiola* rosea extract (200 mg/d) or a placebo 2 times per day for 4-wk. Similar to the results published by Pilaczynska-Szczesniak et al. (144), Skarpanska-Stejnborn et al. (168) described a significant effect of *Rhodiola* rosea extract supplementation on SOD activity as levels were significantly lower immediately and 24-h post-exercise in the *Rhodiola* rosea group compared to placebo. However, contrary to data reported by Pilaczynska-Szczesniak et al. (144) in a similar study cohort, GPx activity was unaffected by supplementation and did not change significantly as a result of the exercise. Skarpanska-Stejnborn et al. (168) also divulged that serum uric acid (UA) and TBARS concentrations significantly increased as a result of the exercise bout and remained elevated above pre-exercise levels at 24-h of recovery, but both were unaffected by differences in supplementation. Continuing to work with trained male rowers of the Polish national team and supplementing with a unique plant superoxide dismutase extract (GliSODin) derived from a SOD-rich melon extract daily (500 mg/d) for 6-wk, Skarpanska-Stejnborn et al. (170) required subjects in this placebo-controlled study to perform a 2,000 m maximum-effort test on a rowing ergometer. GPx levels increased significantly over pre-exercise values immediately post-exercise, but only GPx activity in the GliSODin supplemented group returned to pre-exercise levels at 24-h of recovery. Skarpanska-Stejnborn et al. (170) further reported that SOD activity was significantly greater in the GliSODin group compared to placebo pre-exercise, immediately post-exercise, and 24-h of recovery. TBARS levels were not affected by

supplementation, but concentrations significantly increased over pre-exercise levels immediately following exercise (170).

Lafay et al. (102) employed a crossover design study with a variety of elite male sportsman to investigate the effects of a polyphenol-rich grape extract (400 mg/d) compared to placebo (400 mg/d) supplementation over a 30-d training and competition period. After 30-d of supplementation, Lafay et al. (102) found no significant difference in SOD, catalase, and oxidized LDL activities between groups. However, contrary to the findings reported by Pilaczynska-Szczesniak et al. (144) and Skarpanska-Stejnborn et al. (170) in trained rowers, Lafay et al. (102) described a decrease in GPx activity with placebo supplementation compared to a maintenance of baseline GPx activity with grape extract ingestion. As another oxidative stress and inflammatory biomarker, Lafay et al. (102) also reported a significant increase in urinary excretion of isoprostanes with placebo supplementation compared to no change from baseline values with grape extract ingestion. Utilizing trained cyclists, Morillas-Ruiz et al. (125) had subjects perform a 90-min submaximal endurance time trial on a cycle ergometer while consuming a commercial antioxidant beverage containing fruit concentrates and carbohydrates. Mortillas-Ruiz et al. (125) measured plasma levels of lipid peroxidation through TBARS, indicating a significant increase in TBARS immediately post-exercise only in the placebo group with levels returning to pre-exercise values at 45-min of recovery. Oxidative stress was also measured through protein oxidation (PC) and Mortillas-Ruiz et al. (125) reported a significant polyphenol supplementation-induced decrease in PC levels post-exercise compared to baseline and placebo supplementation.

Across this large collection of endurance exercise studies conducted mostly in trained athletes, researchers found that on the whole, various phytochemical or polyphenol-derived supplements had an attenuating effect on markers of oxidative stress or free-radical production. While there was no similarity across supplements, most of the research reported a decrease in GPx, TBARS, and SOD activity as a result of phytochemical or polyphenol-derived supplementation compared to a placebo. The study conducted in elite male sportsman by Lafay et al. (102) provided conflicting results among the free radical and oxidative stress markers tested that may have been due to the incongruence in the study population or the long duration cross over research design.

Effects of Tart Cherry Supplementation

Ducharme et al. (9) piloted the first endurance-based study to investigate the effects of Montmorency tart cherry juice supplementation on oxidative stress created by an exhaustive incremental treadmill running protocol in thoroughbred horses. Overall indications of exercise-induced oxidative stress were reported through significant elevations in lipid hydroperoxidation decomposition products over time as measured by TBARS (58), but no differences between groups were reported (50). In an endurance study, Howatson et al. (76) examined the effects of tart cherry juice supplementation on oxidative stress following a marathon run. Supplementing with a tart cherry juice blend or placebo for 8-d surrounding the marathon, Howatson et al. (76) demonstrated significantly lower TBARS levels 48-h post-marathon in the tart cherry supplemented group versus placebo. Following the marathon, Howatson et al. (76) contrastingly

demonstrated no significant difference in protein carbonyls (PC) as a marker of protein oxidation between groups. In coordination with Howatson et al. (76), an endurance-based study in trained cyclists conducted by Bell et al. (12) in response to repeated days of high-intensity stochastic cycling reported on a marker formed in the initial stages of lipid peroxidation, serum lipid hydroperoxide (LOOH) (32, 71) was significantly attenuated across the entire trial period with Montmorency cherry concentrate supplementation compared to placebo (13).

The two endurance-based studies conducted in humans agreed on the positive effects of tart cherry supplementation on attenuation of oxidative stress markers and reported similar findings to those stated in the majority of research within the previous section. The reliability of the results derived from the two human-based studies would assume to be high considering that both reports were published out of the same research group. Due to a lack of comparison to other tart cherry supplement studies in race horses, it is difficult to ascertain if these results differed from those in human due to the small study cohort size, previous training status, or differences in acute physiological adaptations to endurance based exercise between race horses and humans.

Free Radical and Oxidative Stress Response to Resistance-Based Exercise

Effects of Antioxidant Vitamins

Childs et al. (32) supplemented previously untrained subjects with either a placebo or a vitamin C (12.5 mg/kg body weight) + N-acetyl-cysteine (NAC) (10 mg/kg body weight) combination for 7-d after a resistance exercise challenge. Within the exercise protocol, subjects were asked to perform 3 sets of 10 repetitions of

eccentrically-resisted elbow flexion exercise at 80% of 1-RM on the non-dominant arm. As a result of the eccentric flexion exercise challenge, Childs et al. (32) described a significant elevation in plasma SOD activity in both treatment groups, with a greater elevation in the vitamin C + NAC group over the course of the 7-d exercise recovery period. Despite a lack of significant elevation in plasma GPx levels above baseline values, Childs et al. (32) found a significantly greater GPx activity 2-d post-exercise in the vitamin C + NAC group compared to placebo. Determining the effects of supplementation on lipid peroxidation, Childs et al. (32) reported increased LOOH levels on days 2, 3, and 4 post-exercise in both groups, but a significant LOOH increase in those ingesting vitamin C + NAC on days 2 and 3 compared to placebo supplementers. Further, 8-isoprostane (8-iso-$PGF_{2\alpha}$) as a marker formed from the oxidation of arachidonic acid, also increased in the plasma as a result of the eccentrically-braked arm flexion exercise with a significant increase following supplementation of the antioxidant combination compared to placebo.

In a more recent, yet similar, study of healthy, untrained males, Bryer and Goldfarb (22) supplemented subjects for 18-d (14-d pre-exercise and 4-d post-exercise) three times daily with either vitamin C (3 g/d) or a placebo. Bryer and Goldfarb (22) had subjects perform 70 eccentrically-resisted elbow flexions on the non-dominant arm with 10-sec rest allotted between repetitions (22). Within this particular study design, oxidative stress was measured through glutathione activity and the ratio of oxidized to total glutathione (GSSG/TGSH). While there was no change evident in the whole blood total glutathione levels over the course of the study, however, Bryer and Goldfarb

reported a significant increase in the GSSG/TGSH ratio at 4-h and 24-h post-eccentric exercise in only the placebo group compared to lower levels in the vitamin C supplemented group. Using a more traditional resistance training exercise in a long duration placebo-controlled protocol, Fischer et al. (57) supplemented a cohort of physically active males with a combination of vitamin C (500 mg/d) and *RRR*-α-tocopherol (400 IU/day) 4-wk prior to and 1-d after a resistance exercise challenge. Subjects performed 3-h of two-legged dynamic knee-extensor exercise at 60 leg extensions per minute at 50% their maximum power output. As a specific measure of plasma lipid peroxidation indicative of overall oxidative stress, Fischer et al. (57) described a stabilization in plasma F_2-isoprostane concentration at pre-exercise levels in those supplementing with the antioxidant vitamin combination versus a significant increase demonstrated in the placebo group during post-exercise recovery.

The two more recent studies that supplemented subjects for a period of approximately 4-wk prior to the resistance-based exercise challenge demonstrated beneficial effects of antioxidant vitamin supplementation through attenuation of post-exercise oxidative stress markers compared to a placebo. Once again, the upper body resistance-based study with ingestion of an antioxidant vitamin combination only in the post-exercise period conducted by Childs et al. (32) produced overwhelmingly conflicting results compared to research supplementing subjects before and after a single strenuous exercise bout. Future research needs to be conducted where the time course of supplementation is varied but the supplement itself remains the same to help clarify any

speculation with respect to antioxidant vitamin supplementation surrounding bouts of resistance-based exercise.

Effects of Phytochemicals and Functional Foods

In an eccentrically-based resistance exercise study, Goldfarb et al. (65) supplemented healthy, college-aged males with a fruit, berry, and vegetable concentrate or placebo twice daily for 4-wks (28-d pre-eccentric exercise, day of, and 4-d post-eccentric exercise) surrounding a session of 4 sets of 12 repetitions of eccentrically-resisted elbow flexions. In a series of blood oxidative stress measurements, Goldfarb et al. (65) reported a significant increase in protein oxidation via PC and malondialdehyde (MDA) in the placebo group over the course of the 72-h recovery period that was different from the baseline-maintained PC levels of the FVC-treated group. Further, lipid hydroperoxide (LOOH) were unaffected by the eccentric exercise bout, thus no difference between groups. Goldfarb et al. (65) also analyzed glutathione status in the subjects through the GSSH/TGSH ratio, revealing that both groups had significantly elevated levels immediately post-eccentric exercise. However, at 6-h post-exercise, the ratio only remained elevated in the placebo group compared to the FVC-treated group, indicating a significant effect of the supplement on this marker of oxidative stress (65).

Examining intramuscular adaptations to a single bout of eccentrically-resisted isokinetic leg extensions on the dominant, Kerksick et al. (94) supplemented healthy, active males for 14-d with either *N*-acetyl-cysteine (NAC) (1,800 mg/d), epigallocatechin gallate (EGCG) (1,800 mg/d), or a placebo. Kerksick et al. (94) assessed oxidative stress through serum concentrations of 8-isoprostane and SOD, but

levels were not affected by differences in supplementation despite a post-exercise increase in serum SOD concentrations.

The contrasting results displayed across these two studies are likely exemplified by major differences in the study supplement, resistance exercise modality used, and duration of supplementation. While the study subject population was similar, there was not any common free-radical or oxidative analyses run between the two studies, making comparison of the results extremely difficult. Future research needs to integrate both upper and lower body eccentrically-resisted exercise in order to start development of conclusive evidence surrounding phytochemical and functional food supplementation when paired with resistance-based exercise.

Effects of Tart Cherry Supplementation

Unlike the protein oxidation results from Howatson et al. (76), the first tart cherry supplemented resistance training study in the literature to analyze hematological markers conducted by Bowtell et al. (20) reported a trend of lower PC 24-h post-eccentric resistance exercise with Montmorency cherry juice supplementation compared to placebo. Bowtell et al. (20), surrounding the intensive resistance exercise workout of repeated leg extensions in resistance trained males, also found no difference in serum NT measures between supplementation groups in the post-strength exercise period. None of the exercise-based tart cherry supplementation studies in the literature tested changes in SOD as a result of the intervention.

As a result of tart cherry supplementation, results of this study begin to define a potential attenuating effect on post-exercise protein oxidation with no differences in

nitric oxide metabolic markers. Although these measures are positive concerning supplementation with tart cherries compared to a placebo, they do not closely align with the aforementioned endurance-based studies. Resistance-based exercise relies less on oxidative mechanisms and mitochondrial function for energy production compared to endurance exercise, thus likely defining the inconsistency in results between resistance and endurance-based tart cherry supplementation studies. Tart cherry supplementation surrounding resistance exercise challenges needs to be studied more extensively moving forward to help build supporting evidence in the literature.

Performance and Muscle Function Recovery in Response to Endurance Exercise

Effects of NSAIDs

Studying the effects of acute ibuprofen supplementation against a placebo in a crossover design study, Donnelly et al. (48) subjected young, healthy, and untrained male volunteers to a 45-min downhill treadmill run at 70% of their estimated maximum heart rate. Subjects ingested either 600 mg of ibuprofen or placebo 30-min prior to the downhill run and an additional 600 mg of supplement every 6-hrs post-run up to 72-h of recovery for a total administration of 8400 mg (48). Expired air was collected during the 45-min run from the 19th to 21st minute and the 39th to 41st minute in addition to the last 2-min of a 5-min pre-run trial using an automated gas analysis system. Supplementation did not have any effect on running speed or oxygen consumption (48). As a result of the endurance performance, Donnelly et al. (48) assessed muscle function of each leg using a MVIC protocol and a measurement of isometric endurance at 50% of MVIC pre-run and at several time points throughout the post-run recovery. The assessment of muscle

function demonstrated a significant decline in isometric muscle strength and 50 percent endurance time throughout the 72-h recovery, but the decline was unaffected by ingestion of ibuprofen compared to placebo (48). In another crossover study with a similar design and subject cohort, Donnelley et al. (49) had volunteers supplement with diclofenac (50 mg) or a placebo 90-min before the previously described downhill running protocol and an additional 50 mg at 8-h intervals up to 72-h post-run. This second study by Donnelley et al. (49) also reported that there was no supplement effect on treadmill running speed and oxygen consumption.

Similar to other research groupings, this pair of endurance exercise studies with NSAID supplementation by Donnelley et al. (48, 49) provides a fairly comprehensive picture due to the utilization of a similar subject cohort and study design. There does not seem to be any effect of NSAID supplementation on running performance and associated makers in untrained males following an intense bout of downhill running.

Effects of Antioxidant Vitamins

An endurance-based training study conducted by Aguiló et al. (2) examined aerobically trained amateur athletes from a variety of specialties in which they supplemented daily for 90-d during their respective competitive seasons with a combination of vitamin E (500 mg/d), β-carotene (30 mg/d), and vitamin C (1,000 mg/d for final 15-d only) compared to a placebo. During this supplementation period, athletes were asked to adhere to their normative training regimen and Aguiló et al. (2) measured changes in maximal and submaximal physiological parameters. All of the subjects within the study that continued their respective training programs over the 90-d study

period improved VO_2 max, maximal blood lactate concentration, and maximal workload attained during the maximal aerobic capacity test on the cycle ergometer (2). However, Aguiló et al. (2) reported that those who supplemented with the antioxidant vitamin combination had a lower blood lactate concentration at maximal workload and attained a greater percentage of VO_2 max at anaerobic threshold compared to placebo. A second antioxidant vitamin supplementation study combined with 8-wks of endurance training in a previously untrained population was conducted by Gomez-Cabrera et al. (67). The researchers supplemented their subjects with either 1000 mg/d of Vitamin C or a placebo over the 8-wk period in which all of the subjects trained 3 times/wk over the course of the study period. Gomez-Cabrera et al. (67) found opposing results compared to the previous study conducted in the endurance trained population by Aguiló et al. (2), demonstrating only an increase in maximal aerobic capacity (VO_2 max) as measured on a cycle ergometer in the placebo group compared to maintenance of pre-intervention capacity in the vitamin C supplemented subjects over the 8-wks. A third study conducted by Kang et al. (89) compared a polyphenol-rich extract derived from litchi fruit with a vitamin C + vitamin E combination on outcomes of aerobic performance following 30-d of supplementation in healthy, recreationally trained endurance subjects. Kang et al. (89) reported that supplementation with the vitamin C (800 mg/d) + vitamin E (1200 IU/d) combination significantly reduced VO_2 max from baseline measures to post-supplementation, while having no effect on both time to exhaustion during a time trial performance and anaerobic threshold.

In an aerobic based crossover study designed to simulate multi-sprint sports, Thompson et al. (183) recruited habitually active males to ingest a vitamin C supplement (1 g dose) or a placebo 2-h prior to a 90-min intermittent shuttle-running test (183). Specifically, the Loughborough Intermittent Shuttle Test (LIST) implemented in this study protocol consists of 90-min variable intensity shuttle running (walking, jogging, and sprinting) over a 20 m distance. Thompson et al. (183) assessed muscle function on both leg extensors and flexors using a five stage test on an isokinetic dynamometer, requiring a series of submaximal, maximal, and isometric flexion/extension contractions. As a result of the post-LIST testing, muscle function in the leg extensors did not change significantly from baseline or between supplementation trials (183). However, Thompson et al. (183) did report a drop in leg flexor function of both legs during the isometric and slower isokinetic sets up to 48-h post-LIST of the vitamin C supplemented trial. In another placebo-controlled, running-based study conducted by Thompson et al. (184) within the same year in physically active males, supplementation of vitamin C or placebo was carried out for 14-d surrounding a prolonged 90-min high-intensity intermittent shuttle running test (LIST). Subjects were supplemented twice daily (morning and evening) with vitamin C (400 mg/d) or a placebo. Thompson et al. (184) utilized a similar muscle function test as the previous study, reporting that both leg extensors and flexors demonstrated a decrease in peak torque production below pre-exercise levels during both isometric and concentric contractions. However, peak torque in the leg flexors tended to be greater with vitamin C supplementation in the post-exercise period.

Given the large body of evidence within this section, the effects of antioxidant vitamin supplementation on performance variables was highly inconsistent even among two similar intermittent shuttle-based endurance studies conducted by Thompson et al. (183, 184). The inconsistency is likely derived from the variation in antioxidant supplement combinations, supplement ingestion timelines, and subject training status. Due to the large differences in study results, it is difficult to draw overarching conclusions concerning antioxidant vitamin supplementation effects on endurance exercise performance variables.

Effects of Phytochemicals and Functional Foods

Perhaps one of the most frequently researched phytochemical and polyphenol supplements in relation to changes in exercise performance are quercetin supplements due to their longer half-life within blood circulation (127). Utilizing a pre-test/post-test control group design in recreationally active male subjects, Cureton et al. (43) supplemented their study cohort 1 time/d over a variable time period of 7-16-d with a sports hydration beverage that contained 1g quercetin. The study subjects were aerobically tested pre/post supplementation using both a 10-min maximal work cycling test followed by a 1-h bout of moderate intensity cycling (43). As a result of the study testing, Cureton et al. (43) determined that there was no statistically significant pre-treatment to post-treatment changes in VO_2 peak, perception of effort during the submaximal cycling test, and total work done throughout the 10-min maximal effort cycling bout between quercetin and placebo supplementation groups. In a crossover study of healthy, untrained subjects in which the subjects were supplemented with a

beverage containing 500 mg quercetin or simply the beverage as a placebo twice daily (1000 mg/d total quantity) for 7-d, Davis et al. (44) implemented both a cycling VO_2 max test (supplementation day 7) and a cycling endurance ride to exhaustion (supplementation day 8) at the end of each treatment period. As a result of 7-d of supplementation, Davis et al. (44) reported a significant increase in both cycling VO_2 max and ride time to exhaustion in the quercetin group compared to placebo. In a second quercetin and exercise crossover study published in the same year as Davis et al. (44), Ganio et al. (62) supplemented untrained, sedentary males and females with either a placebo or quercetin-containing (1000 mg/d) food bar for 5-d. Ganio et al. (62) reported that 5-d of quercetin supplementation did not influence VO_2 max or any other related cardiorespiratory variables, even when accounting for gender, compared to a placebo.

Moving away from utilizing a VO_2 max test as the primary measure of performance or cardiovascular improvement, two other studies took a different approach. Similar to some of the previous quercetin research, Nieman et al. (132) employed untrained volunteers, specifically young adult males, in this crossover design. Study volunteers were supplemented for 2-wk with quercetin (1000 mg/d) or a placebo that were made undetectable by dissolving supplements in sugarless PowerAde (132). As the measure of performance, study volunteers performed a preload treadmill exercise protocol that involved a 60-min run at 60% VO_2 max with a 10% treadmill grade (132). This preload protocol was then followed by a 12-min treadmill time trial at a 15% grade at a self-selected speed and previous research has determined that this particular protocol

is a more consistent method of performance determination compared to a time trial. Nieman et al. (132) demonstrated that those volunteers supplemented with quercetin achieved greater net change in running distance compared to placebo. MacRae and Mefferd (112) took a different approach compared to some of the previously published quercetin research as they first used elite cyclist as volunteers. In this particular crossover design, the cyclists were supplemented twice daily for 6-wk with either an antioxidant beverage containing green tea extract (300 mg), vitamin C (150 mg), and vitamin E (50 mg) or the same antioxidant beverage plus quercetin (300 mg) (112). No placebo was used as a basis of comparison in this particular study. MacRae and Mefferd (112) showed similar performance results as Nieman et al. (132) as consumption of the antioxidant supplement containing quercetin significantly improved the overall 30 km time trial performance in addition to greater performance over the last 5 km of the time trial. Further, cyclists ingesting quercetin-containing antioxidant supplements demonstrated greater average and relative peak power compared to the other antioxidant supplement (112).

Phytochemicals and polyphenols are typically derived from whole fruits or fruit-based supplements, but it is most common to see studies analyzing a fruit extract compared to a fruit juice (127). In one of the few polyphenol-rich juice and exercise supplementation studies other than those using tart cherry juice, Pilaczynska-Szczesniak et al. (144) recruited male members of the Polish rowing team to ingest 50 mL of chokeberry juice or placebo three times daily (150 mL/d) over the course of their 4-wk training camp. At the beginning and end of the training camp, the crew athletes

performed a 2000-m rowing test where maximal power achieved during the test reached 450-500 W. After 1-d rest, the subjects performed an incremental rowing session that was broken down into 3-min pieces with increasing percentage of maximal power required with each progressing rowing piece (144). Although no performance-based measurements were reported, Pilaczynska-Szczesniak et al. (144) demonstrated via finger stick method a significantly lower blood lactate level with chokeberry supplementation compared to placebo. As one of the polyphenol fruit extract studies measuring changes in performance as an outcome variable, Kang et al. (89) recruited healthy, recreationally trained aerobic Koreans to receive either oligomerized lychee fruit extract (OLFE) (200 mg/d), a vitamins C + E mixture (800 mg vitamin C + 1200 IU vitamin E/d), or a placebo (200 mg/d) twice per day for 30-d. Subjects were required to perform a submaximal (80% HR_{max}) treadmill running test to exhaustion and a graded treadmill VO_2 max test as part of the study protocol (89). Kang et al. (89) described a significant increase in submaximal endurance time to exhaustion from baseline to post-supplementation in only the OLFE group with no change in maximal oxygen consumption. However, after supplementation, the subjects that supplemented with OLFE demonstrated a significant increase in anaerobic threshold compared to no significant changes in the vitamin and placebo groups (89).

Within the quercetin-based supplementation and endurance exercise challenge studies, the majority of evidence seems to support an increase in performance-related variables as a result of quercetin supplementation compared to a placebo. Two quercetin supplementation and endurance performance studies did report no significant

performance differences when compared to a placebo. However, the first study conducted by Cureton et al. (43) supplemented subjects on a variable time scale from 7-16-d potentially contributing to inconsistent results. The second study in question published by Ganio et al. (62), supplemented subjects with a food-based supplement containing quercetin compared to all other studies that supplemented subjects through liquid-based ingestion. With minimal additional phytochemical and functional food-based studies beyond quercetin supplementation, there still seems to be some evidence that this type of longer-term supplementation (4-wk) may also be beneficial to increasing aerobic performance outcomes over placebo supplementation.

Effects of Tart Cherry Supplementation

The endurance running-based Montmorency cherry juice supplementation versus placebo trial conducted by Howatson et al. (76) surrounding a full marathon reported that the difference between predicted finish time and actual race finish time was greater in the placebo group (19 min discrepancy) compared to the tart cherry juice group (7 min discrepancy) despite never reaching significance. This performance-related trend is interesting considering that there was no statistically significant differences between groups on highest weekly training mileage, longest training run, and number of previous marathons (e.g. marathon experience) (76). Further, Howatson et al. (76) also tested the effects of supplementation on maximal voluntary isometric contractions (MVICs) following the marathon race using a standardized protocol on the non-dominate leg that included three submaximal 3-sec trials (50%, 70%, 90% of perceived max) followed by two maximal isometric 3-sec trials. Howatson et al. (76) reported a decrement in MVIC

strength following the marathon compared to baseline levels that was similar across groups, however, there was significantly faster recovery of strength over the 48-h post-race period with tart cherry juice supplementation versus placebo.

This single marathon study with short-term tart cherry supplementation supports the evidence described in the previous section of phytochemical and functional food research as both endurance performance seemed to be faster with supplementation along with quicker recovery of muscular strength recovery in the post-exercise period. Additional research needs to be continued in this area of short-term tart cherry supplementation surrounding bouts of strenuous endurance performance to help confirm the aforementioned findings published by Howatson et al. (76).

Performance and Muscle Function Recovery in Response to Resistance Exercise

Effects of NSAIDs

Employing a counter-balanced, double-blinded study design to analyze the effects ibuprofen supplementation over the course of 6-wk of contralateral biceps training, Krentz et al. (100) recruited college-aged males and females with previous resistance training experience. Subjects trained each arm on alternative days, 5-d/wk over a 6-wk training period in while they randomly received ibuprofen (400 mg/d) or a placebo immediately post-workout corresponding to arm training pattern. Elbow flexor strength was assessed by Krentz et al. (100) through a 1-RM concentric concentration curl test. As a result of the training, Krentz et al. (100) reported no effect of ibuprofen supplementation on elbow flexor strength measures compared to placebo.

Attempting to ascertain the effects of ibuprofen supplementation on markers of muscle injury and performance following a bout of eccentrically-resisted arm curls, Pizza et al. (145) designed a crossover study using a small cohort of sedentary males. Pizza et al. (145) supplemented subjects with either ibuprofen (2400 mg/d) or placebo for a total of 15-d (5-d pre-exercise and 10-d post-exercise). The primary resistance exercise performed was 25 repetitions of a single arm, eccentrically-resisted arm curl. Muscle function and performance was assessed using a 4-sec duration MVIC protocol with the arm bent at 90° elbow flexion (145). Joint angle integrity (relaxed and flexed) was also measured using a standard goniometer. Pizza et al. (145) reported no difference in average and peak force developed during the eccentric arm exercise between treatments. Further, MVIC strength and joint angle integrity (relaxed and flexed) decreased significantly following the eccentric exercise bout, but the measurements were not significantly different between treatments (145). Rahnama et al. (152) recruited and randomly assigned non-athletic male subjects to one of four study groups: physical activity, ibuprofen, physical activity + ibuprofen, or control. The physical activity groups performed 20-min of warm-up activity prior to the eccentric exercise. DOMS-inducing exercise involved performance of 70 eccentric arm-curl contractions 3-sec in duration at 80% MVC with 12-sec rest between eccentric repetitions. Rahnama et al. (152) measured muscular performance through comparison of maximum eccentric contraction and discovered that the reduction from baseline levels in maximal eccentric performance in the control and ibuprofen groups was significantly greater compared to the physical activity (24-h and 48-h post-exercise) and combination

(48-h post-exercise) groups. Muscular performance returned to baseline levels at 48-h post-eccentric exercise in the physical activity and combination groups, but still remained significantly depressed below baseline in the control and ibuprofen groups.

In an earlier resistance-based NSAID supplement study, Hasson et al. (72) employed healthy, untrained males and females to complete a 10-min bout of repeated bench step-ups with additional load of 10% body weight. Subjects were either supplemented with 3 doses of ibuprofen (1200 mg) over 24-h starting 4-h pre-exercise (prophylactic), a single dose of ibuprofen (400 mg) at 24-h post-exercise (therapeutic), placebo, or a control receiving no treatment. Using an isokinetic dynamometer, Hasson et al. (72) assessed muscular performance through concentric and eccentric knee extension peak torque production at 60°/sec over 5 repetitions on the left leg. Knee extension MVICs were also measured at 60° of knee flexion over three attempts also on the left leg. Similar to the muscle soreness results, Hasson et al. (72) reported a significant attenuation in isometric force decline with prophylactic ibuprofen supplementation compared to the other three treatment groups at 24-h post-exercise. Both ibuprofen groups significantly attenuated the isokinetic concentric and eccentric contraction performance as well as MVIC decline at 48-h post-exercise compared to the placebo and control groups.

As a common characteristic between all four of these studies, ibuprofen was used as the NSAID supplement surrounding each bout of resistance-based exercise. Despite this similarity, the results and effectiveness of ibuprofen supplementation on resistance exercise performance and recovery of post-exercise muscle function was equivocal.

While three studies employed an eccentrically-resisted arm curls as their exercise protocol, only two found similar non-significant results with regard to ibuprofen supplementation compared to placebo. The final study mentioned in this section conducted by Hasson et al. (72) utilized a lower body step-up protocol as the method of fatiguing exercise, which may have been a significant contributor to the difference in results compared to the other three upper-body resistance-based studies. Another source of variability between studies potentially contributing to the inconsistent results was the discrepancy in volume and dosage of ibuprofen ingestion across all four studies. Additional research needs to be performed to help clarify these study discrepancies and solidify supporting or refuting evidence for NSAID supplementation to help improve resistance exercise performance and recovery.

Effects of Antioxidant Vitamins

In a placebo-controlled study conducted with healthy, non-resistance trained men, Beaton et al. (8) supplemented subjects for 30-d with either vitamin E (1200 IU/d) or a placebo. Within this particular study, subjects performed an isokinetic protocol that compromised of 24 sets of 10 eccentrically-resisted knee extension/flexion contractions (8). As a measure of muscle strength and integrity, Beaton et al. (8) also had subjects perform 5-sec duration MVICs and 3 reps of maximal, low velocity isokinetic leg extensions pre-eccentric exercise and at several post-eccentric exercise time points. Beaton et al. (8) reported that despite torque values that fell below pre-exercise values over the course of the eccentric exercise recovery period, there were no significant differences between groups for any of the aforementioned torque measures. Further,

there was no change or difference between supplementation groups in thigh diameter when measured at the largest mid-thigh circumference point as a gross measure of edema following the eccentric exercise bout (8). In a second study conducted on healthy, untrained males, Bryer and Goldfarb (22) supplemented subjects for 18-d (14-d pre-exercise and 4-d post-exercise) three times daily with either vitamin C (3 g/d) or a placebo. Bryer and Goldfarb (22) had subjects perform 70 eccentrically-resisted elbow flexions on the non-dominant arm with 10-sec rest allotted between repetitions. As part of the assessment protocol, subjects performed three MVCs on both their dominant and non-dominant arms to determine maximum isometric force pre-eccentric exercise and at several post-eccentric exercise time points (22). Post-eccentric exercise testing revealed a significant reduction in maximal isometric force and range of motion across the 96-h recovery with similar patterns of force loss and progression back to baseline among the supplement groups (22). Supplementing moderately active and healthy male volunteers for 37-d with a combination of vitamin C (500 mg/d) and vitamin E (1200 IU/d) or a placebo, Shafat et al. (167) employed an exercise protocol comprised of 30 sets of 10 eccentric knee extensions on their dominant leg using an isokinetic dynamometer. As part of the assessment protocol, subjects performed three MVICs on their dominant leg to determine maximal contraction force of the knee extensors pre-eccentric exercise and at several post-eccentric exercise time points (167). Analysis of peak concentric torque production, total work, and maximal isometric force production revealed that there was a significant decline in all three measures post-eccentric exercise, but this decline was significantly attenuated with the vitamin C + E supplementation combination compared

to placebo (167). Despite the positive effects on muscle function, there were no significant differences between groups reported with changes in thigh volume, thus muscle edema, despite an overall volume increase as a result of the eccentric exercise bout when measured around the thigh at its largest point of circumference (167).

Similar to previous positive reports in this literature review, the vitamin C + E supplementation combination reported beneficial effects in post-eccentric exercise performance recovery compared to a placebo. These results reported by Shafat et al. (167) were not supported by the other two studies that described no significant differences in functional performance recovery when only supplementing with vitamin C or vitamin E. While the duration of vitamin supplementation is different among each of the studies, with the longest time period being most effective, it does not seem justified that this would be the primary cause of the large discrepancy in results. Future research must focus on combining all three antioxidant vitamin supplementation combinations into a single resistance-based study to help clarify the results reported across these three individual studies.

Effects of Phytochemicals and Functional Foods

A crossover study of elite male athletes from varying athletic endeavors was conducted by Lafay et al. (102). This particular research group was interested in investigating the effects of a polyphenol-rich grape extract (400 mg/d) compared to placebo (400 mg/d) supplementation over a 30-d training and competition period on physical performance (102). Lafay et el. (102) measured repeated jumping force capacity at baseline and post-supplementation, reporting a significant improvement in

jumping force capacity (physical performance) and explosive power in the handball athlete group (n=10) with grape extract supplementation over placebo. In an acute eccentric exercise-based crossover study, Trombold et al. (189) recruited recreationally active males who were supplemented twice daily with either a pomegranate juice (960 mL/d) or a placebo (960 mL/d) over a 9-d period (4-d pre-exercise, day of, and 4-d post-exercise) surrounding the exercise bout. The single eccentric exercise bout involved two sets of 20 maximal eccentric elbow flexions in which subjects were required to resist an isokinetic dynamometer for 3-sec followed by a 15-sec rest per repetition (189). Measurement of elbow flexion strength was assessed using an isometric strength test at both 150° and 135° of elbow flexion. Trombold et al. (189) reported that strength loss was similar between groups 2-h post-exercise and did not completely recover to baseline measures even at 96-h post-exercise. However, supplementation with pomegranate juice seemed to hasten strength recovery as strength was significantly greater at 48-h and 72-h of recovery compared to placebo (189).

In a more recent pomegranate juice supplementation study, Trombold et al. (190) supplemented resistance-trained men surrounding a single workout of both unilateral resisted eccentric elbow flexion and knee extension exercises. Subjects were supplemented twice daily with either a pomegranate juice (500 mL/d) or a placebo (500 mL/d) over a 15-d period (7-d pre-exercise, day of, and 7-d post-exercise) surrounding the exercise bout (190). The single eccentric exercise bout involved three sets of 20 maximal eccentrically resisted elbow flexions on an isokinetic dynamometer (performed as described in the previous study (189)) and six sets of 10 unilateral eccentrically

resisted (3-sec count) knee extensions at 110% unilateral 1-RM on a traditional isotonic leg extension machine (190). Measurement of elbow flexion (30° and 45° above full elbow extension) and knee extension (45° and 90° below full knee extension) strength were assessed using isometric strength tests. Utilizing these isometric strength tests, Trombold et al. (190) reported significantly greater isometric elbow flexion strength throughout the 168-h recovery period in the pomegranate group compared to placebo, but no differences between supplementation groups were shown in isometric knee extension strength despite a common post-eccentric exercise isometric strength loss. In the same publication year, Goldfarb et al. (65) published a study in a cohort of healthy, college-aged volunteers that supplemented with a fruit, berry, and vegetable concentrate or placebo twice daily for 4-wks (28-d pre-eccentric exercise, day of, and 4-d post-eccentric exercise). This propriety blend of fruit, vegetable, and berry powder concentrates provided a source of β-carotene (7.5 mg/d), vitamin C (276 mg/d), and vitamin E (108 IU/d), in addition to a natural source of flavonoids and anthocyanins (65). Subjects were required to perform 3-sec MVICs with both their dominant and non-dominant elbow flexors on an isokinetic dynamometer at baseline, pre-exercise, and several post-exercise time points (65). The eccentric exercise performed consisted of four sets of 12 repetitions of eccentrically resisted elbow flexions on the non-dominant arm at 20°/sec angular velocity (65). Unlike the performance results reported by Trombold et al. (189) in the initial pomegranate juice study, Goldfarb et al. (65) demonstrated a similar drop in non-dominant arm elbow flexor MVIC and range of

motion between groups following the eccentric exercise bout with no between group differences up to 72-h of recovery.

Examining intramuscular adaptations to a single bout (100 repetitions: 10 sets of 10 repetitions) of eccentrically-resisted isokinetic leg extensions on the dominant leg, Kerksick et al. (94) supplemented healthy, active males for 14-d with either *N*-acetyl-cysteine (NAC) (1,800 mg/d), epigallocatechin gallate (EGCG) (1,800 mg/d) as a catechin and polyphenol combination derived from green tea, or a placebo. Muscle strength was assessed isometrically on the dominant leg where 3 individual leg extension MVICs were each completed over 5 seconds at 90° of flexion (94). Peak isometric torque was significantly lower compared to baseline values at 6-h and 24-h post-exercise, but no difference was exhibited across supplementation groups.

While there seems to be some promising results with respect to faster strength recovery and muscle function utilizing some of the phytochemical and food-derived supplements, there is not conclusive evidence across the majority of studies described in this section. As previously mentioned, the lack of conclusive evidence is likely due to the differences in supplement as each phytochemical and food-derived supplement has a unique composition of polyphenols and other antioxidant compounds that may alter the supplements effectiveness when ingested surrounding a resistance exercise bout. For this reason, individual phytochemicals and functional food-derived components should be investigated both individually and synergistically to help derive the safest and most effective naturally-based supplement. Future research directions may also need to focus on directly comparing different phytochemical or food-derived supplements in response

to both resistance and endurance exercise challenges to help clarify potential mechanisms.

Effects of Tart Cherry Supplementation

Within the eccentric exercise and resistance-related literature, Connolly et al. (40) conducted a crossover study on healthy college-aged males that were supplemented with a tart cherry juice blend or a placebo two times per day for 8-d surrounding a bout of 40 maximal eccentric elbow flexion contractions. Relaxed end point range of motion for the elbow flexors at the elbow joint was measured by via a standard goniometer. Despite an overall elbow range of motion loss over the 96-h post-exercise recovery, no significant difference was reported between groups (40). Similar to the recovery performance assessment by Howatson et al. (76) following marathon running, Connolly et al. also measured isometric elbow flexion strength, performing two 3-sec maximal isometric trials at each elbow angle (130°, 90°, and 30°). Connolly et al. (40) reported that overall isometric elbow flexion strength loss was significantly attenuated in the tart cherry supplement group compared to placebo when strength measures were averaged across all isometric test angles. In more recent resistance-based crossover study in trained athletes, Bowtell et al. (20) supplemented these subjects for 10-d surrounding a bout of single-leg leg extensions with either Montmorency tart cherry juice or a placebo. Similar to the two previous studies, Bowtell et al. (20) measured knee extension maximal voluntary contractions (MVCs) pre-exercise, immediately, 24-h, and 48-h post-exercise using an inline force transducer calculating force over 1-sec periods. As reported in the previous study by Connolly et al. (40) with elbow flexor force

production, a significant drop in post-exercise force production was demonstrated by this cohort, but pre-exercise normalized MVC force recovery occurred significantly faster with tart cherry juice concentrate versus placebo over the 48-h recovery period (20).

These two resistance-based tart cherry studies reported attenuated the loss of post-exercise strength and expedited recovery of muscle function. Both of these studies demonstrate that short-term tart cherry supplementation surrounding a bout of resistance-based exercise can be an effective recovery aid following both upper and lower body dominant resistance exercise. The results of these studies resonate with the expedited muscle function recovery results reported following a marathon run, demonstrating a universal effectiveness with tart cherry supplementation across various exercise modalities. Future research would be best suited to focus on confirming the results of these studies and comparing multiple forms of tart cherry supplementation within the same study design.

CHAPTER III

METHODS[*]

Tart Cherry Resistance

Overall Study Design

This study was conducted in a randomized, double-blind, and placebo-controlled manner utilizing two treatment groups. All subjects eligible to participate in the study completed a morning familiarization session where they were provided detailed information regarding the study design, testing procedures, and supplementation protocols. Approximately 10-d prior to the resistance exercise intervention, eligible subjects returned to the lab for a morning baseline testing session to determine body weight, height, and body composition. Following baseline measurements subjects were matched based on relative maximal back squat strength, fat free mass, body weight, and age and randomly separated into two groups: 1) a placebo group (P) or 2) a powdered tart cherry group (TC). Dietary intake was not controlled, but subjects were asked to not change their dietary habits in any way throughout the study (upon start of supplementation). This was monitored by subject documentation of dietary intake for 4-d of the first 7 supplementation days prior to the resistance exercise challenge. Subjects were also instructed to maintain their normal resistance training program on study days where physical activity was not restricted (e.g. up to 48-h prior to each testing session).

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[*]Portions reprinted from "Effects of powdered Montmorency tart cherry supplementation on an acute bout of intense lower body strength exercise in resistance trained males" by Levers K, Dalton R, Galvan, E, et al. 2015. *Journal of the International Society of Sport Nutrition*, 12, 1-23, Copyright 2015 by Kyle Levers.

Independent and Dependent Variables

The independent variable of interest was the type of supplement ingested. Dependent variables were quadriceps muscle soreness perception; serum markers of mechanical muscle damage, secondary muscle damage, and physiological stress; serum markers of the anabolic and catabolic hormone response; serum markers of the inflammatory and anti-inflammatory response; serum markers of free radical production, oxidative stress, and antioxidant activity; whole blood immune cell counts; and recovery strength performance. Table 1 lists the components specifically examined for each independent variable.

Study Site

All laboratory testing was conducted in the Exercise & Sport Nutrition Laboratory. This laboratory is based in the Department of Health and Kinesiology and College of Education and Human Development at Texas A&M University in College Station, Texas.

Subjects

Twenty-three (23) healthy, resistance-trained men (20.9±2.6 yr, 14.2±5.4% body fat, 63.9±8.6 kg FFM) participated as subjects in this study. Recruited subjects were required to have been involved in a progressive resistance training program that included regular squat exercise for at least six months prior to study recruitment and to be able to perform a standard barbell back squat in a power rack of at least 1.5 times their body weight. Figure 1 demonstrates the breakdown of the subject population as it pertains to the study progression. Discontinuation of any subject

participation was not related to any aspect of the supplementation or testing protocol. All subjects signed informed consent documents and the study was approved by the Texas A&M University Institutional Review Board prior to any data collection. Subjects were not allowed to participate in this study if they reported any of the following: 1) any metabolic disorders or taking any thyroid, hyperlipidemic, hypoglycemic, anti-hypertensive, anti-inflammatory (e.g. NSAIDs), and/or androgenic medications; 2) history of hypertension, hepatorenal, musculoskeletal, autoimmune, and/or neurological disease(s); 3) allergy to cherries or any cherry components (e.g. polyphenols, anthocyanins, anthocyanidins). Using this study exclusion criteria, 33 resistance-trained subjects qualified to participate in this study (see Figure 1) out of 86 total men screened.

Experimental Design

Figure 2 shows the experimental design to be used in this study. The study was conducted in a randomized, double-blind, and placebo-controlled manner. All subjects eligible to participate in the study completed a morning familiarization (FAM) session where they were provided detailed information regarding the study design, testing procedures, and supplementation protocols. Informed consent, medical history, and endurance training history questionnaires were also completed during the familiarization session. A research nurse reviewed medical history documents and performed a physical exam on each subject to ensure safety and participation eligibility. A fasting blood sample was taken at the end of the familiarization session if the subject met entrance criteria as a pre-supplementation reference.

Table 1: Study Dependent Variables [Resistance]

Muscle Soreness Perception	Pro-Inflammatory Cytokines & Chemokines	Anti-Inflammatory Cytokines	Free Radical Production & Oxidative Stress	Antioxidant Status	Muscle Catabolism	Physiological Stress & Secondary Muscle Damage	Anabolic & Catabolic Hormone Status	Whole Blood Immune Cell Counts	Recovery Strength Performance
Vastus	TNF-α	IL-4	TBARS	TAS	CK	AST	Cortisol	WBC	Isokinetic MVCs
Medialis (¼)	IFN-γ	IL-5	NT			ALT	Testosterone	LYMPH	
	IL-1β	IL-7	SOD			Creatinine	Test/Cortisol	GRAN	
Vastus	IL-2	IL-10				Urea/BUN	Ratio	MID	
Lateralis (¼)	IL-6	IL-13				BUN/Creatinine		Hemoglobin	
	IL-8					Ratio		HCT	
Vastus	IL-12					Total Protein		RBC	
Lateralis (½)						Total Bilirubin		GM-CSF	
						Uric Acid			

Abbreviations: IK = isokinetic; MVC = maximal voluntary contraction; AST = Aspartate aminotransferase; ALT= Alanine aminotransferase; BUN = Blood urea nitrogen; CK = Creatine kinase; Test/Cortisol = Testosterone/Cortisol ratio; TBARS = Thiobarbituric acid reactive substances; TAS = Total antioxidant status; SOD = Superoxide dismutase; TNF-α = Tumor necrosis factor alpha; IFN-γ = Interferon gamma; IL = interleukin; WBC = White blood cell; LYMPH = Lymphocytes; MID = Mid-range absolute count; GRAN = Granulocyte absolute count; GM-CSF = Granulocyte-macrophage colony-stimulating factor

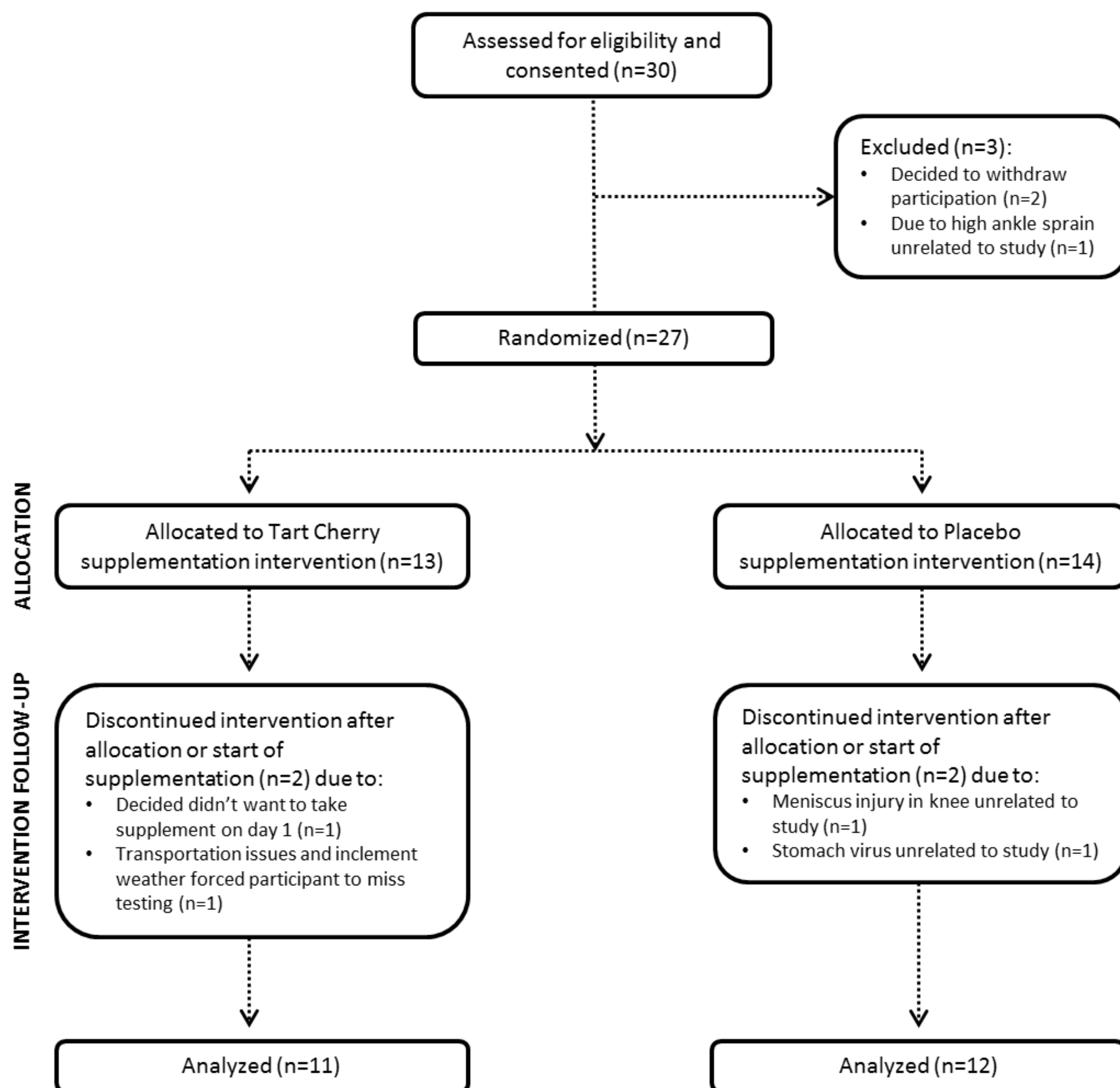

Figure 1. Tart Cherry Resistance Study Population Consort Diagram

Subjects were asked to not change their dietary habits in any way throughout the study (upon start of supplementation). This was monitored by subject documentation of dietary intake for 4-d (3 weekdays and 1 weekend day) of the first 7 supplementation

days prior to the resistance exercise challenge. Ten days (10-d) prior to the resistance exercise intervention, eligible subjects returned to the lab for a morning baseline testing session (BASE) to determine body weight, height, and body composition. The subjects then were familiarized with the maximal voluntary contraction (MVC) protocol using their dominant leg on the isokinetic knee extension dynamometer followed by a 5-min recovery before determination of their barbell back squat 1-reptetion maximum (1-RM) in a power rack/smith machine. Following baseline measurements subjects were matched based on relative maximal back squat strength, fat free mass, body weight, and age and randomly separated into two groups: 1) a placebo group or 2) a powdered tart cherry group.

Subjects were instructed to begin supplementation 7-d prior to the resistance exercise challenge (Day 0). Subjects were asked to fast overnight for 10-h to account for diurnal variations as well as abstain from exercise and consumption of NSAIDs for 48-h prior to all testing days. On the day of the resistance exercise challenge, the subjects reported to the lab where body weight, resting heart rate, and resting blood pressure were measured. Subjects then donated a fasting venous blood sample (approximately 20 ml) using standard clinical procedures to measure pre-run effects of supplementation on all hemodynamic variables and rated perceptions of muscle soreness to a standardized application of pressure on their dominant thigh at 3 designed locations using a graphic pain rating scale (GPRS). The subjects then completed the MVC protocol using their dominant leg on the isokinetic dynamometer followed by a 5-min recovery before the barbell back squat protocol was completed with a Tendo power and speed analyzer

attached to the bar. Fasting (except 60-min post-lift) blood samples, GPRS ratings of quadriceps muscle soreness, and the isokinetic leg extension MVC protocol were completed at 60-min, 24-h and 48-h post-lift recovery. The last day of supplementation correlated with 48-h post-lift recovery.

Tart Cherry Resistance Exercise Protocol

Isokinetic Knee Extension Maximal Voluntary Contractions

At baseline, before the squat exercise, 60-min after the squat exercise, 24-h and 48-h post-lift exercise, subjects performed an isokinetic knee extension MVC test using their dominant leg on a Kin-Kom 125AP Isokinetic Dynamometer (*Chattanooga-DJO Global Inc., Vista, CA, USA*). During the baseline familiarization of the isokinetic leg extension MVC protocol, standard procedures were used to determine and record proper subject positioning on the Kin-Kom to ensure accurate repeatability of the testing protocol across all five sessions. The subject warmed-up on the isokinetic dynamometer by performing 3-sets of 5 repetitions of dominant knee extension/flexion at 50% of their MVC (determined during the familiarization) with 1-min recovery between sets. After the 1-min recovery following the third warm-up set, the subject performed 3 knee extension/flexion MVCs in succession with no rest between contractions. Subjects were allotted a 5-min recovery between the isokinetic MVC and barbell back squat protocols. Test to test variability of performing this test yielded average C_V values of ±8.47% with a test retest correlation of r=0.88.

Barbell Back Squat 1-Repetition Maximum Determination

At baseline (BASE), following the 5-min recovery after the isokinetic MVCs, subjects performed 3-sets of 5 repetitions of the barbell back squat on a Smith Machine (*Life Fitness, Schiller Park, IL, USA, model SSM)* at 50% of their anticipated 1-RM with 2-min recovery between sets. Following the warm-up protocol, the barbell back squat 1-RM was determined on the Smith Machine using a standard 1-RM protocol defined by the National Strength and Conditioning Association (NSCA) with 2-min recovery periods between 1- repetition sets of increasing weight. All 1-RM determinations were made within 3-5 sets beyond the warm-up. In order to successfully complete each set, the subject was required to reach parallel as determined by a NSCA Certified Strength and Conditioning Coach providing a verbal "up" cue during spotting.

Barbell Back Squat Exercise Protocol

On Day 8, following the 5-min recovery after the isokinetic MVCs, subjects performed 1 warm-up set of 10 repetitions of the barbell back squat at 50% 1-RM (determined during BASE). After 3-min recovery, the subjects performed 10 sets of 10 repetitions of barbell back squat at 70% 1-RM with 3-min recovery between sets. A TENDO Power and Speed Analyzer (*TENDO Sports Machines, Trencin, Slovak Republic, model PSA310*) was attached to the bar during all 100 repetitions to be completed during the squat protocol to determine peak power, average force, and total work for each repetition. Following the squat protocol, subjects were only permitted to stretch with limited ambulation until the 60-min post-lift testing protocol was completed.

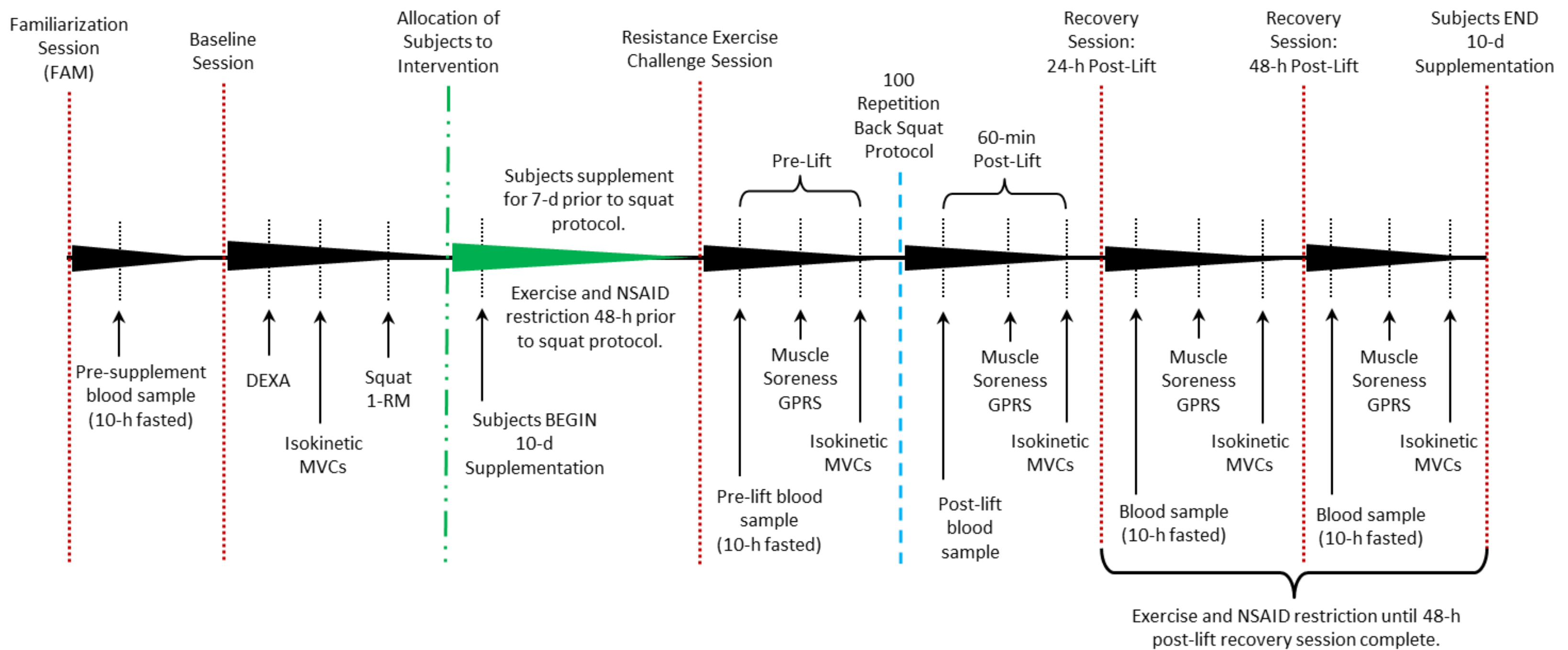

Figure 2. Tart Cherry Resistance Study Research Design Schematic
DEXA = dual-energy X-Ray absorptiometer, MVC = maximal voluntary contraction, 1-RM = 1-repetition maximum, NSAID = non-steroidal anti-inflammatory drugs, GPRS = graphic pain rating scale, 7-d = 7-day, 48-h = 48-hour.

Tart Cherry Endurance

Overall Study Design

This study was conducted in a randomized, double-blind, and placebo-controlled manner utilizing two treatment groups. All subjects eligible to participate in the study completed a morning familiarization session where they were provided detailed information regarding the study design, testing procedures, and supplementation protocols. Ten days (10-d) prior to the endurance exercise intervention, eligible subjects returned to the lab for a morning baseline testing session to determine body weight, height, and body composition. Following baseline measurements subjects were matched based on average reported race pace, fat free mass, body weight, and age and randomly separated into two groups: 1) a placebo group (P) or 2) a powdered tart cherry group (TC). Dietary intake was not controlled, but subjects were asked to not change their dietary habits in any way throughout the study (upon start of supplementation). This was monitored by subject documentation of dietary intake for 4-d of the first 7 supplementation days prior to the endurance exercise challenge. Subjects were also instructed to maintain their normal exercise training program on study days where physical activity was not restricted (e.g. 48-h prior to each testing session).

Independent and Dependent Variables

The independent variable of interest was the type of supplement ingested. Dependent variables include serum markers of mechanical muscle damage, secondary muscle damage, and physiological stress; serum markers of the anabolic and catabolic hormone response; serum markers of the inflammatory and anti-inflammatory response;

serum markers of free radical production, oxidative stress, and antioxidant activity; whole blood immune cell counts; serum clinical markers of health; quadriceps muscle soreness perception; and endurance race running performance. Table 2 lists the components specifically examined for each independent variable.

Study Site

The tart cherry study half-marathon race course was completed on a previously planned road course on the campus of Texas A&M University in College Station, Texas (see Appendix G). All laboratory testing was conducted in the Exercise & Sport Nutrition Laboratory. This laboratory is based in the Department of Health and Kinesiology and College of Education and Human Development at Texas A&M University in College Station, Texas.

Subjects

27 endurance trained runners or triathlete (21.8±3.9 yr, 15.0±6.0% body fat, 67.4±11.8 kg) men (n=18) and women (n=9) participated as subjects in this study. To ensure training intensity and volume consistency, we aimed to recruit endurance runners or triathletes from those respective Texas A&M club teams. All recruited subjects were required to be involved in a consistent running program for at-least one-year and able to run a half-marathon (21.1 km) in less than 2 hours. Figure 3 demonstrates the breakdown of the subject population as it pertains to the study progression. Discontinuation of any subject participation was not related to any aspect of the supplementation or testing protocol.

Table 2: Study Dependent Variables [Endurance]

Muscle Soreness Perception	Pro-Inflammatory Cytokines & Chemokines	Anti-Inflammatory Cytokines	Free Radical Production & Oxidative Stress	Antioxidant Status	Muscle Catabolism	Physiological Stress & Secondary Muscle Damage	Anabolic & Catabolic Hormone Status	Whole Blood Immune Cell Counts	Endurance (½ Marathon) Running Performance
Vastus	TNF-α	IL-4	TBARS	TAS	CK	AST	Cortisol	WBC	Split Time
Medialis (¼)	IFN-γ	IL-5	NT			ALT	Testosterone	LYMPH	Finish Time
	IL-1β	IL-7	SOD			Creatinine	Test/Cortisol	GRAN	Proj. Race Pace
Vastus	IL-2	IL-10				Urea/BUN	Ratio	MID	Actual Race Pace
Lateralis (¼)	IL-6	IL-13				BUN/Creatinine		Hemoglobin	
	IL-8					Ratio		HCT	
Vastus	IL-12					Total Protein		RBC	
Lateralis (½)						Total Bilirubin		GM-CSF	
						Uric Acid			

Abbreviations: IK = isokinetic; MVC = maximal voluntary contraction; AST = Aspartate aminotransferase; ALT= Alanine aminotransferase; BUN = Blood urea nitrogen; CK = Creatine kinase; Test/Cortisol = Testosterone/Cortisol ratio; TBARS = Thiobarbituric acid reactive substances; TAS = Total antioxidant status; SOD = Superoxide dismutase; TNF-α = Tumor necrosis factor alpha; IFN-γ = Interferon gamma; IL = interleukin; WBC = White blood cell; LYMPH = Lymphocytes; MID = Mid-range absolute count; GRAN = Granulocyte absolute count; GM-CSF = Granulocyte-macrophage colony-stimulating factor; Proj. = Projected

All subjects signed informed consent documents and the study will be approved by the Texas A&M University Institutional Review Board prior to any data collection. Subjects were not allowed to participate in this study if they reported any of the following: 1) any metabolic disorders or taking any thyroid, hyperlipidemic, hypoglycemic, anti-hypertensive, anti-inflammatory (e.g. NSAIDs), and/or androgenic medications; 2) history of hypertension, hepatorenal, musculoskeletal, autoimmune, and/or neurological disease(s); 3) allergy to cherries or any cherry components (e.g. polyphenols, anthocyanins, anthocyanidins). Using this study exclusion criteria, 34 endurance-trained subjects qualified to participate in this study (see Figure 1) out of 62 total individuals screened.

Experimental Design

Figure 4 outlines the experimental design used in this study. The study was conducted in a randomized, double-blind, and placebo-controlled manner. All subjects eligible to participate in the study completed a morning familiarization session where they were provided detailed information regarding the study design, testing procedures, and supplementation protocols. Informed consent, medical history, and endurance training history questionnaires were also completed during the familiarization session. A research nurse reviewed medical history documents and perform a physical exam on each subject to ensure safety and participation eligibility. A fasting blood sample was taken at the end of the familiarization session if the subject met entrance criteria as a pre-supplementation reference. Subjects were asked to not change their dietary habits in any way throughout the study (upon start of supplementation). This was monitored by

subject documentation of dietary intake for 4-d (3 weekdays and 1 weekend day) of the first 7 supplementation days prior to the resistance exercise challenge. Ten days (10-d) prior to the endurance exercise challenge, eligible subjects returned to the lab for a morning baseline testing session to determine body weight, height, and body composition. Following baseline measurements subjects were matched based on average reported/projected race pace, fat free mass, body weight, and age and randomly separated into two groups: 1) a placebo group or 2) a powdered tart cherry group.

Subjects were instructed to begin supplementation 7-d prior to the endurance exercise challenge (Day 0). Subjects were asked to fast overnight for 10-h to account for diurnal variation as well as abstain from exercise and consumption of non-steroidal anti-inflammatory medications (NSAIDs) for 48-h prior to all testing days. On the day of the endurance exercise challenge, subjects reported to the lab where body weight, resting heart rate, and resting blood pressure will be measured. Subjects then donated a fasting venous blood sample (approximately 20 ml) using standard clinical procedures to measure pre-run effects of supplementation on all hemodynamic variables and rated perceptions of muscle soreness to a standardized application of pressure on their dominant thigh at 3 designed locations using a graphic pain rating scale (GPRS). Twenty minutes prior to the start of the half-marathon race, subjects were allowed to warm-up as they normally would before running a road race. Subjects completed a half-marathon (21.1 km) run outdoors at their normal race/competition pace. Both water and glucose-electrolyte drinks, individually labeled for each runner to match their race bib

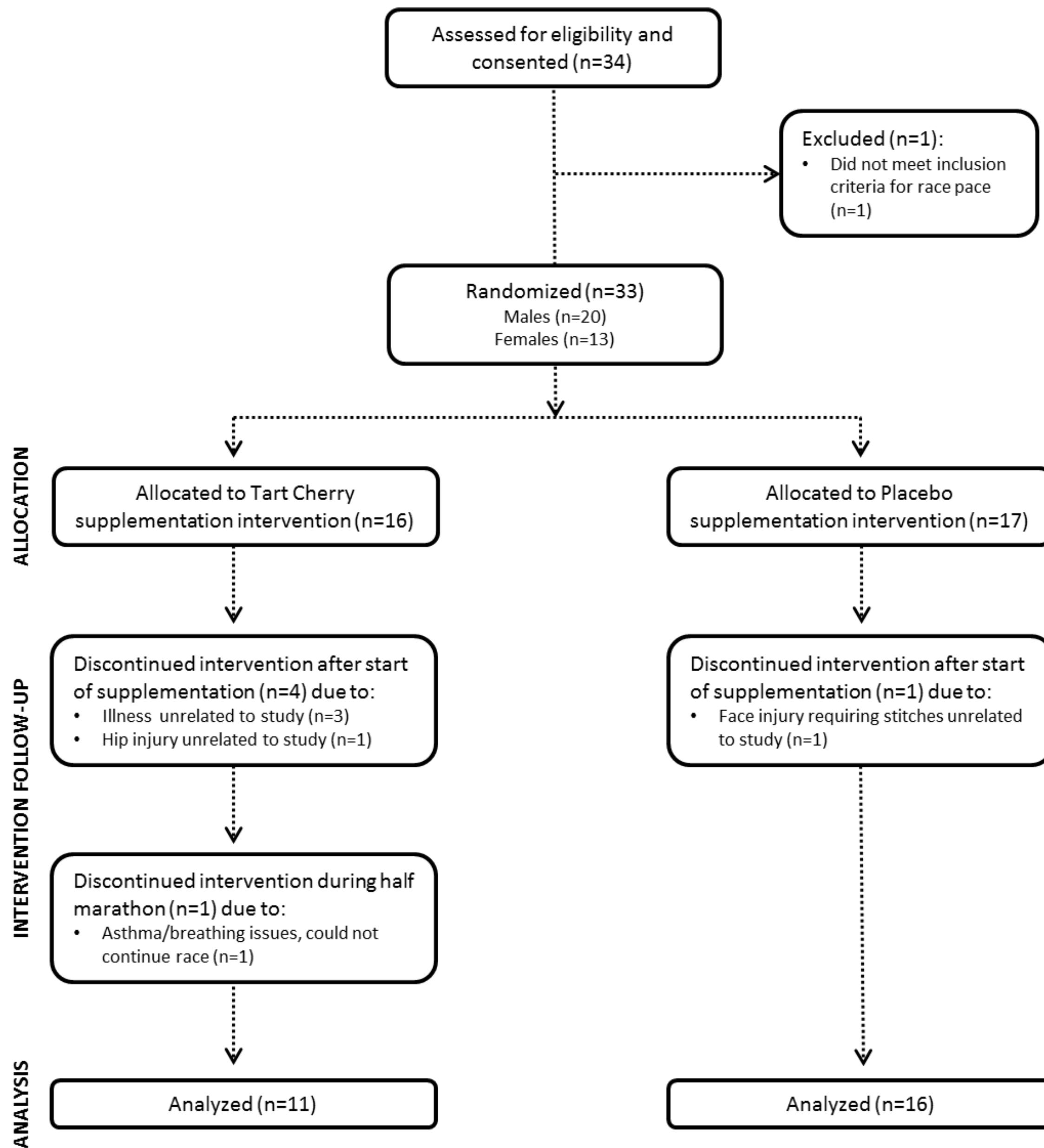

Figure 3. Tart Cherry Endurance Study Population Consort Diagram

number, were provided to the runners at four individually spaced intervals during the race.

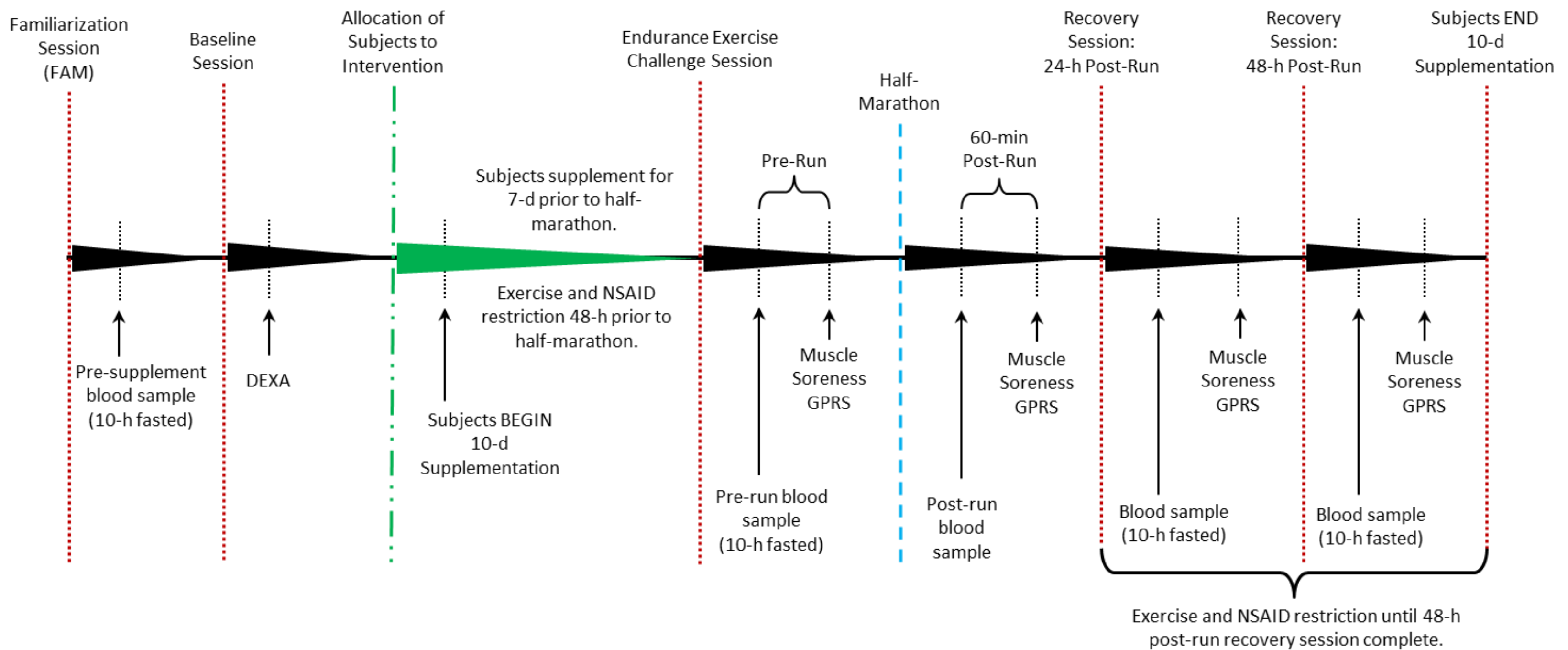

Figure 4. Tart Cherry Endurance Study Research Design Schematic
DEXA = dual-energy X-Ray absorptiometer, MVC = maximal voluntary contraction, 1-RM = 1-repetition maximum, NSAID = non-steroidal anti-inflammatory drugs, GPRS = graphic pain rating scale, 7-d = 7-day, 48-h = 48-hour.

Fasting (except 60-min post-run) blood samples and GPRS ratings of quadriceps muscle soreness were completed at 60-min, 24-h and 48-h of post-run recovery. The last or tenth day of supplementation correlated with 48-hours post-run recovery.

Tart Cherry Endurance Exercise Protocol

Half-Marathon (21.1 km) Run

On the morning of supplementation endurance exercise challenge, all subjects performed an outdoor half-marathon (21.1 km) run together on a planned and closed Texas A&M University campus course under simulated race day conditions (see Appendix G). The race course was planned completely on concrete and pavement surfaces. All subjects were given 20-min for individual warm-up routines before the start of the half-marathon. At regular intervals (4 total locations) throughout the race, fluids (water and/or glucose-electrolyte beverages) were made available to the runners. Each runner had their own water and glucose-electrolyte beverage bottle labeled with a number that corresponds to their race bib number. All fluid bottles were weighed before and after the race to determine fluid consumption for each subject. Official race splits and finish times were recorded by designated lab staff. Following the race, subjects were not allowed to run to cool down, only stretching and minimal ambulation was permitted until the 60-min post-run testing session.

Tart Cherry Resistance and Endurance Common Study Methods

Supplementation Protocol

Subjects were assigned in a double-blinded and randomized manner to ingest a rice flour placebo (P) or powdered tart cherry (TC). Subjects were matched into one of the two groups according to the previously described criteria listed for each study. Subjects were instructed to ingest the supplements with breakfast at 0800 for 7-d prior to, the day of, and for 2-days following the respective exercise challenge (resistance or endurance) for a total supplementation timeline of 10-d. The tart cherry supplements contained 480 mg of freeze dried Montmorency tart cherry skin powder derived from tart cherry skins obtained after juicing (*CherryPURE™ Freeze Dried Tart Cherry Powder, Shoreline Fruit, LLC, Transverse City, MI, USA*). Prior analytical testing conducted in 2012 by Atlas Bioscience (Tuscon, AZ, USA) demonstrated that 290 mg of *CherryPURE™* provides at least 600 mg of phenolic compounds and 40 mg of anthocyanins per serving, which is equivalent to consuming 10.5 fluid ounces of tart cherry juice. Based on the results of the previous analytical testing, the 480 mg/d *CherryPURE™* dosage supplemented in the current studies provides at least 993 mg of phenolic compounds and 66 mg of anthocyanins per serving/day. The supplements were prepared for distribution by Shoreline Fruit, LLC and sent to Advanced Laboratories (*Salt Lake City, UT, USA*) to quantify total phenolic compound and anthocyanin content of the powdered tart cherry supplements. Both supplements were prepared in

standardized color capsules and packaged in generic bottles by Shoreline Fruit, LLC for double blind administration.

Tart Cherry Resistance and Endurance Common Study Procedures

Dietary Inventories

Within the first 7-d of supplementation, subjects were instructed to record all food and fluid intake over a 4-d period (3 weekdays, 1 weekend day), which is reflective of their normal dietary intake. Dietary inventories were then reviewed by a registered dietician and analyzed for average energy, macronutrient, and dietary antioxidant intake using Food Processor (*Version 8.6*) Nutritional Analysis software (*ESHA Research Inc., Salem, OR, USA*).

Anthropometrics and Body Composition

At the beginning of every testing session, subjects had their height and body mass measured according to standard procedures using a Healthometer Professional 500KL (*Pelstar LLC, Alsip, IL, USA)* self-calibrating digital scale with an accuracy of ±0.02 kg. Whole body bone density and body composition measures (excluding cranium) was determined with a Hologic Discovery W Dual-Energy X-ray Absorptiometer (DEXA; *Hologic Inc., Waltham, MA, USA*) equipped with APEX Software (*APEX Corporation Software, Pittsburg, PA, USA*) by using procedures previously described (1, 98). Mean test-retest reliability studies performed on male athletes in our lab with this DEXA machine have revealed mean coefficients of variation for total bone mineral content and total fat free/soft tissue mass of 0.31-0.45% with a

mean intraclass correlation of 0.985 (43). On the day of each test, the equipment was calibrated following the manufacturer's guidelines.

Muscle Soreness Perception Assessment

Pressure application to the three specified areas of the quadriceps muscle group on the subject's dominant leg was standardized to 50 N of pressure using a handheld Commander Algometer (*JTECH Medical, Salt Lake City, UT, USA*). The standard amount of pressure was applied to the vastus lateralis (VL) at both 25% and 50% of the distance between the superior border of the patella to the greater trochanter of the femur at the hip and to the vastus medalis (VM) at 25% of the distance between the aforementioned landmarks. These three specific locations were measured and marked with a permanent marker on each participant during the baseline muscle soreness perception measurement before the exercise challenge (resistance or endurance). The participants were asked to maintain these 3 marked locations between testing sessions to avoid error with secondary measurement. The subject was seated in a reclined supine position and given the algometer GPRS sheet to evaluate the perception of muscle soreness at each of the three quadriceps locations. The order of pressure application was standardized across all sessions and participants: 25% VM, 25% VL, and 50% VL. The 50 N of pressure was applied to a relaxed quadriceps at each of the 3 locations using the algometer for a period of 3-sec to give the subject enough time to record their soreness evaluation on the GPRS. Perceptions of muscle soreness were recorded by measuring the distance (centimeters) of the participant mark on the GPRS from 0 cm (no pain).

Blood Collection

Subjects were required to fast (except for the 60-min post-exercise session) for 10-h prior to donating approximately four teaspoons (20 milliliters) of venous blood from an antecubital vein using standard phlebotomy procedures. Blood analyzed for markers of muscle damage, oxidative stress, inflammation, and clinical chemistry panels were collected in two 7.5 mL BD Vacutainer® serum separation tubes (*Becton, Dickinson and Company, Franklin Lakes, NJ, USA)*, left at room temperature for 15-min, and then centrifuged at 3500 rpm for 10-min using a standard, refrigerated (4°C) bench top Thermo Scientific Heraeus MegaFuge 40R Centrifuge (*Thermo Electron North America LLC, West Palm Beach, FL, USA).* Serum supernatant was removed and stored at -80°C in polypropylene microcentrifuge tubes for later analysis. Blood was also collected in a single 3.5 mL BD Vacutainer® lavender top tube containing K_2 EDTA (*Becton, Dickinson and Company, Franklin Lakes, NJ, USA)*, left at room temperature for 15-min, and refrigerated for approximately 3-4 h before complete blood count analysis.

Clinical Chemistry Analysis

Whole blood samples were analyzed for complete blood count with platelet differentials (hemoglobin, hematocrit, red blood cell counts (RBC), white blood cell counts (WBC), lymphocytes, granulocytes (GRAN), and mid-range absolute count (MID) using a Abbott Cell Dyn 1800 (*Abbott Laboratories, Abbott Park, IL, USA*) automated hematology analyzer. The internal quality control for Abbott Cell Dyn 1800

was performed using three levels of control fluids purchased from the manufacturer to calibrate acceptable standard deviation (SD) and coefficients of variation (C_V) values for all aforementioned whole blood cell counts. Serum samples were analyzed using a Cobas c111 (*Roche Diagnostics GmbH, Indianapolis, IN, USA*) automated clinical chemistry analyzer that was calibrated and optimized according to manufacturer guidelines. This analyzer has been known to be highly valid and reliable in previously published reports (19). Each serum sample was assayed for a standard partial metabolic panel [(aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin)] and clinical markers of protein and fatty acid metabolism [(uric acid, creatinine, blood urea nitrogen (BUN), BUN:creatinine ratio, total protein, and creatine kinase (CK)]. The internal quality control for the Cobas c111 was performed using two levels of control fluids purchased from the manufacturer to calibrate acceptable SD and C_V values for all aforementioned assays. Samples were re-run if the observed values were outside control values and/or clinical norms according to standard procedures.

Markers of Anabolic/Catabolic Hormone Status

Serum samples were assayed using standard commercially available enzyme-linked immunosorbent assay kits (ELISAs) for cortisol and testosterone (*ALPCO Diagnostics, Salem, NH, USA*) hormone analysis. Serum concentrations were determined calorimetrically using a BioTek ELX-808 Ultramicroplate reader (*BioTek Instruments Inc., Winooski, VT, USA*) at an optical density of 450 nm against a known

standard curve using manufacturer recommended procedures. Samples were run in duplicate according to standard procedures to ensure validity of measurement.

Markers of Oxidative Stress

Serum samples were assayed using standard commercially available ELISA kits for Superoxide Dismutase (SOD Activity Assay kit), Total Antioxidant Status (TAS, Antioxidant Assay kit), Thiobarbituric Acid Reactive Substance (TBARS, Malondialdehyde-MDA, TCA method kit) (*Cayman Chemical Company, Ann Arbor, MI, USA*), and Nitrotyrosine (*ALPCO Diagnostics, Salem, NH, USA*). Serum concentrations for SOD and Nitrotyrosine were determined calorimetrically using a BioTek ELX-808 Ultramicroplate reader (*BioTek Instruments Inc., Winooski, VT, USA*) at an optical density of 450 nm against a known standard curve using standard procedures. Serum concentrations for TAS were also determined calorimetrically using a BioTek ELX-808 Ultramicroplate reader (*BioTek Instruments Inc., Winooski, VT, USA*) at an optical density of 405 nm against a known standard curve using standard procedures. Lastly, serum concentrations for TBARS were also determined fluorometrically using a SpectraMax Gemini multimode plate reader (*Molecular Devices LLC, Sunnyvale, CA, USA*) at an excitation wavelength of 530 nm and an emission wavelength of 550 nm against a known standard curve using standard procedures. Samples were run in duplicate according to standard procedures to ensure validity of measurement.

Cytokine/Chemokine Markers of Inflammation

Serum markers of inflammation [(interleukin-1β (IL-1β), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF)] were measured by using a commercially available Milliplex MAP 13-Plex Human High Sensitivity T-Cell Magnetic Bead Panel kit (*EMD Millipore Corporation, St. Charles, MO, USA*) that is optimized for human serum samples. A minimum of 100 positive beads for each cytokine/chemokine is acquired with a Luminex MagPix instrument (*Luminex Corporation, Austin, TX, USA*). This instrument has been proven to be highly valid and reliable in previously published reports across many disciplines (52, 83, 107, 201). Manufacture supplied controls were used to monitor the coefficients of variation. Samples were run in duplicate according to standard procedures to ensure validity of measurement.

Statistical Analysis

Individual group and time data presented throughout the dissertation text and in all tables as means (± SD), while group effects will be presented as means (± SEM). All related variables were grouped and analyzed using repeated measures MANOVA in IBM SPSS Statistics Software version 22.0 for Windows (*IBM Corporation, Armonk, NY, USA*) to assess values observed and changes from pre-exercise levels in response to the supplement administered. Any collected study variables determined to potentially affect study outcomes of other independent variables were implemented as a covariate in

subsequent ANCOVA analyses to ensure that significant changes reported are due to differences in supplementation treatment. Post-hoc LSD pairwise comparisons were used to analyze any significance among groups where needed with Cohen's d calculations employed to determine effect magnitude. Data was considered statistically significant when the probability of error was less than 0.05 and will be considered to be trending when the probability of error was less than 0.10. Statistical trends ($p<0.05$ to $p<0.10$) were noted as is common practice in studies with relatively small sample size (165).

CHAPTER IV

RESULTS[*]

Tart Cherry Resistance

Subject Baseline Characteristics

A total of 23 healthy, resistance-trained men completed the protocol for this study. Participants were 20.9±2.6 years, 81.7±10.3 kg, 14.2±5.4% body fat, and 63.9±8.6 kg fat free mass. Participant demographic data are presented in Table 3. One-way ANOVA revealed no significant differences ($p>0.05$) in baseline demographic markers. No significant differences in back squat 1-RM ($p=0.70$) and relative squat strength ratio ($p=0.85$) were reported across groups, hence the groups were generally well matched and differences observed. One-way ANOVA analysis also demonstrated no differences in total work performed ($p=0.79$) across groups, indicating that similar work was performed during the exercise intervention and differences can likely be attributed to the nutritional intervention.

Nutritional Intake and Compliance

Nutritional intake was monitored over a 4-d period within the first 7-d of supplementation. Relevant nutritional components analyzed are listed in Table 4. No statistically significant interactions were observed across groups with respect to dietary intake.

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[*]Portions reprinted from "Effects of powdered Montmorency tart cherry supplementation on an acute bout of intense lower body strength exercise in resistance trained males" by Levers K, Dalton R, Galvan, E, et al. 2015. *Journal of the International Society of Sport Nutrition*, 12, 1-23, Copyright 2015 by Kyle Levers.

Table 3: Demographics by Study Group [Resistance]

Variable	Group	Mean	Group (SEM)	p-value
N	P	12	n/a	n/a
	TC	11	n/a	
	Total	23	n/a	
Age (yrs)	P	20.58 ± 1.78	0.51	0.593
	TC	21.18 ± 3.34	1.01	
	Total	20.87 ± 2.60	0.54	
Height (cm)	P	177 ± 5.28	1.52	0.651
	TC	178 ± 10.71	3.23	
	Total	177 ± 8.17	1.70	
Weight (kg)	P	82.62 ± 7.39	2.13	0.659
	TC	80.64 ± 13.16	3.97	
	Total	81.67 ± 10.35	2.16	
Baseline HR (bpm)	P	61.17 ± 10.40	3.00	0.195
	TC	66.09 ± 6.67	2.01	
	Total	63.52 ± 8.98	1.87	
BMD (g/cm^2)	P	1.16 ± 0.10	0.03	0.389
	TC	1.12 ± 0.14	0.04	
	Total	1.14 ± 0.12	0.02	
LM (kg)	P	61.41 ± 4.87	1.41	0.970
	TC	61.55 ± 11.16	3.36	
	Total	61.48 ± 8.27	1.73	
FFM (kg)	P	63.83 ± 5.06	1.46	0.981
	TC	63.92 ± 11.64	3.51	
	Total	63.87 ± 8.62	1.80	
FM (kg)	P	11.81 ± 5.44	1.57	0.595
	TC	14.10 ± 13.58	4.09	
	Total	12.90 ± 10.00	2.08	
Body Fat (%)	P	15.31 ± 6.27	1.81	0.338
	TC	13.09 ± 4.31	1.30	
	Total	14.25 ± 5.42	1.13	
Back Squat 1-RM (kg)	P	144.2 ± 28.1	8.18	0.696
	TC	138.8 ± 37.2	11.21	
	Total	142.0 ± 32.2	6.72	
Relative Squat Strength Ratio	P	1.75 ± 0.27	0.08	0.855
	TC	1.73 ± 0.34	0.10	
	Total	1.74 ± 0.30	0.06	
Workout Total Work (kJ)	P	0.68 ± 0.14	0.04	0.798
	TC	0.70 ± 0.23	0.07	
	Total	0.69 ± 0.18	0.04	

Mean data expressed as means ± SD. One-way ANOVA p-levels listed for each variable: * represents $p<0.05$ difference between groups, § represents $p<0.10$ difference between groups. HR = heart rate; BMD = bone mineral density; LM = lean mass; FFM = free-fat mass; FM = fat mass; 1-RM = 1-Repetition maximum.

Muscle Soreness Perception Assessment

Table 5 presents perceptions of muscle soreness across the resistance exercise protocol. The overall MANOVA analysis revealed a significant overall Wilks' Lambda time (p<0.001) interaction and a non-significant overall group x time effect (p=0.20). Perception of muscle soreness in all three muscle testing locations irrespective of group significantly increased over time, peaking 48-h post-lift, indicating the onset of muscle soreness as a result of the lifting protocol. A significant difference between groups over time was found in vastus lateralis (¼) soreness perception (p=0.024) where ratings increased by 55-170% from pre-lift values in P, but only 35-104% in TC over the recovery. Post-hoc analysis indicated a significantly attenuated increase in muscle soreness perception 24-h post-lift for TC supplementing subjects compared to P (see Figure 5). Effects of supplementation tended to be different in the perception of vastus medialis (¼) soreness (p=0.10) with significantly lower muscle soreness in TC versus P up to 48-h post-lift (see Figure 5). Soreness perception ratings in the vastus medialis (¼) increased by 28-83% from pre-lift values in P, but ranged from a 6% decrease to only a 58% increase in TC over the recovery.

Isokinetic Maximal Voluntary Contraction Performance Assessment

Table 6 reports the total work performed during the 3-repetition isokinetic flexion/extension MVC test. The overall MANOVA analysis revealed both a non-significant Wilks' Lambda time interaction (p=0.96) and a non-significant group x time effect (p=0.75). The 3-repetition work summation univariate measures for extension

(p<0.001), flexion (p=0.022), and total (p<0.001) demonstrated significant changes over time, with the lowest work attained 60-min post-lift in all three measures. No aspect of the isokinetic strength recovery work performed demonstrated a significant group effect over time. While changes from pre-lift were not statistically significant between groups across time, the drop in 3-repetition summation of flexion (p=0.21; d=0.45), extension (p=0.23; d=0.45), and total work (p=0.15; d=0.55) performed 60-min post-lift demonstrates a likely attenuation with a larger n-size in TC compared to P based upon

Table 4: Dietary Analysis by Study Group [Resistance]

Variable	Group	Mean	Group (SEM)	p-value
Average Daily Caloric Consumption (kcal)	P	2617 ± 721	208	0.605
	TC	2455 ± 753	227	
	Total	2540 ± 724	151	
Dietary Protein (g)	P	147.86 ± 43.13	12.45	0.871
	TC	153.06 ± 100.39	30.27	
	Total	150.35 ± 74.28	15.49	
Dietary Carbohydrates (g)	P	244.47 ± 62.58	18.07	0.460
	TC	223.52 ± 70.90	21.38	
	Total	234.45 ± 66.01	13.76	
Dietary Fat (g)	P	84.54 ± 23.55	6.80	0.427
	TC	95.23 ± 38.55	11.62	
	Total	89.65 ± 31.35	6.54	
Dietary Beta-Carotene (mcg)	P	2954 ± 3436	992	0.651
	TC	2111 ± 5260	1586	
	Total	2551 ± 4320	901	
Dietary Vitamin C [Ascorbic Acid] (mg)	P	80.79 ± 65.99	19.05	0.199
	TC	50.56 ± 38.41	11.58	
	Total	66.33 ± 55.55	11.58	
Dietary Vitamin E [Alpha-Tocopherol] (mg)	P	5.91 ± 6.04	1.74	0.910
	TC	6.24 ± 7.44	2.24	
	Total	6.07 ± 6.59	1.37	

Mean data expressed as means ± SD. One-way ANOVA p-levels listed for each variable: * represents p<0.05 difference between groups, § represents p<0.10 difference between groups.

Table 5: Quadriceps Muscle Soreness Perception [Resistance]

Variable	Group	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
Algo I (cm)	P	4.34 ± 2.52	5.53 ± 3.15	7.78 ± 2.93	7.94 ± 2.92	6.40 ± 0.76	*G*=0.139	
	TC	3.80 ± 2.86	3.59 ± 2.76	5.50 ± 2.68	5.99 ± 3.59	4.72 ± 0.79	*T*<0.001*	T_L<0.001*
	Time Mean	4.07 ± 0.56	4.56 ± 0.62	6.64 ± 0.59$^{\Psi\Diamond}$	6.96 ± 0.68$^{\Psi\Diamond}$		*G X T*=0.236	*G X* T_q=0.172
Algo II (cm)	P	2.44 ± 1.60	3.76 ± 2.24$^{\Psi}$	6.60 ± 2.99^$^{\Psi\Diamond}$	6.20 ± 3.64$^{\Psi\Diamond}$	4.75 ± 0.69	*G*=0.773	
	TC	2.98 ± 2.70	4.03 ± 2.93$^{\Psi}$	4.76 ± 3.03$^{\Psi}$	6.07 ± 3.67$^{\Psi\Diamond\#}$	4.46 ± 0.72	*T*<0.001*	T_L<0.001*
	Time Mean	2.71 ± 0.46	3.90 ± 0.54$^{\Psi}$	5.68 ± 0.63$^{\Psi\Diamond}$	6.14 ± 0.76$^{\Psi\Diamond}$		*G X T*=0.187	*G X* T_q=0.024*
Algo III (cm)	P	3.25 ± 2.65	3.42 ± 3.24	6.55 ± 3.80	6.18 ± 3.36	4.85 ± 0.81	*G*=0.609	
	TC	2.68 ± 2.67	3.76 ± 3.18	4.89 ± 3.87	5.64 ± 3.74	4.24 ± 0.85	*T*<0.001*	T_L<0.001*
	Time Mean	2.96 ± 0.55	3.59 ± 0.67	5.72 ± 0.80$^{\Psi\Diamond}$	5.91 ± 0.74$^{\Psi\Diamond}$		*G X T*=0.427	*G X* T_L=0.690

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the participant soreness perception in the quadriceps muscle group at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.199). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. Algo I = Algometer location #1: Vastus Medalis 1/4; Algo II = Algometer location #2: Vastus Lateralis 1/4; Algo III = Algometer location #3: Vastus Lateralis 1/2; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

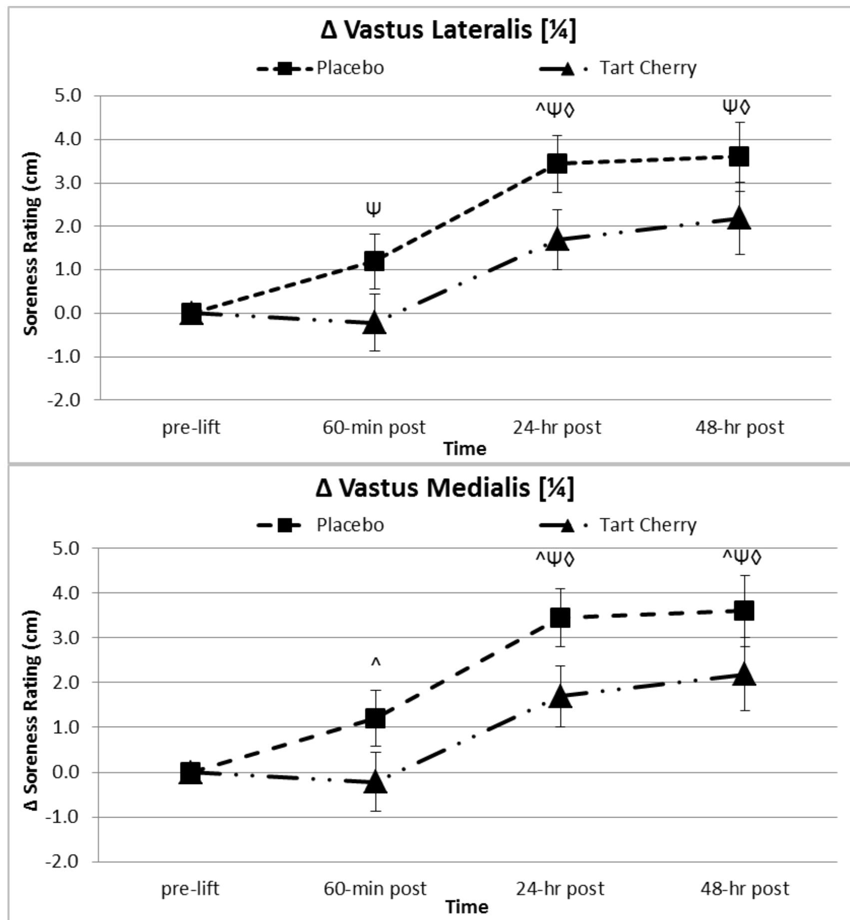

Figure 5. Perceptions of Muscle Soreness [Resistance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-lift, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

the moderate to large Cohen's d effect size calculations. Average recovery decreases in flexion, extension, and total work performance from pre-lift values were 5%, 19%, and 14% respectively in P, but only 2%, 16%, and 10% in TC.

Table 6: Isokinetic Maximal Voluntary Contraction Knee Extension/Flexion Total Work Performance [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
IK Total Extension Work (N)	P	1791 ± 207	1682 ± 235	1278 ± 275	1408 ± 296	1387 ± 291	1509 ± 90	*G*=0.870	
	TC	1757 ± 378	1612 ± 437	1298 ± 422	1418 ± 463	1352 ± 383	1487 ± 94	*T*<0.001*	T_L<0.001*
	Time Mean	1774 ± 295	1648 ± 340†	1288 ± 345^{†Ψ}	1413 ± 376$^{†Ψ◊}$	1370 ± 331^{†Ψ}		*G X T*=0.792	*G X* T_q=0.662
IK Total Flexion Work (N)	P	971 ± 126^	962 ± 141^	913 ± 174^	925 ± 153^	910 ± 113^†	936 ± 58	*G*=0.181	
	TC	1073 ± 252	1060 ± 277	1064 ± 225	1058 ± 305	1010 ± 289†	1053 ± 61	*T*=0.087§	T_L=0.022*
	Time Mean	1020 ± 199	1009 ± 218	986 ± 210	989 ± 242	958 ± 217^{†Ψ}		*G X T*=0.663	*G X* T_q=0.206
IK Total Work (N)	P	2762 ± 293	2644 ± 354	2191 ± 388	2333 ± 407	2296 ± 373	2445 ± 141	*G*=0.646	
	TC	2829 ± 611	2673 ± 687	2363 ± 603	2476 ± 733	2362 ± 644	2540 ± 148	*T*<0.001*	T_L<0.001*
	Time Mean	2794 ± 462	2658 ± 527†	2273 ± 498^{†Ψ}	2401 ± 577$^{†Ψ◊}$	2328 ± 509^{†Ψ}		*G X T*=0.692	*G X* T_q=0.470

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the isokinetic MVC knee extension and flexion performance each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.960) and group x time (p=0.748). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. IK = isokinetic; MVC = maximal voluntary contraction; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Markers of Mechanical Damage and Physiological Stress

Table 7 presents the serum mechanical damage and physiological stress markers tested in the standard clinical safety panel. The overall MANOVA analysis revealed a significant overall Wilks' Lambda time ($p<0.001$) effect, but no difference between groups over time ($p=0.50$). Univariate measures for uric acid ($p<0.001$), total bilirubin ($p=0.026$), creatinine ($p=0.003$), and total protein ($p<0.001$) demonstrated significant changes over time, peaking 60-min post-lift. CK ($p=0.025$) and AST ($p=0.003$) also significantly changed over time, peaking 24-h post-lift. Significant group differences over time and group by time changes from pre-lift were reported for creatinine ($p=0.030$, delta $p=0.024$) and total protein ($p=0.018$, delta $p=0.006$). Analyzing the change from pre-lift levels, significant differences across groups for creatinine ($p=0.007$) and total protein ($p=0.004$) were also evident. Serum creatinine increased on average 2% over pre-lift values during the recovery in P, but actually decreased 7% below pre-lift in TC. Serum total protein increased 2-9% over pre-lift values during the recovery in P, but decreased 0-4% below pre-lift in TC. Subsequent post-hoc analysis indicated a significantly attenuated TC creatinine response 48-h post-lift and a TC total protein level that never differed from pre-lift measures 60-min and 48-h post-lift compared to deviations in P (see figure 6). Increases in serum CK levels tended to be lower in TC over time compared to P ($p=0.10$). Serum CK levels increased on average 135% over pre-lift values during the recovery in P, but increased only 98% in TC. No other significant differences between groups over time or deviations from normal human

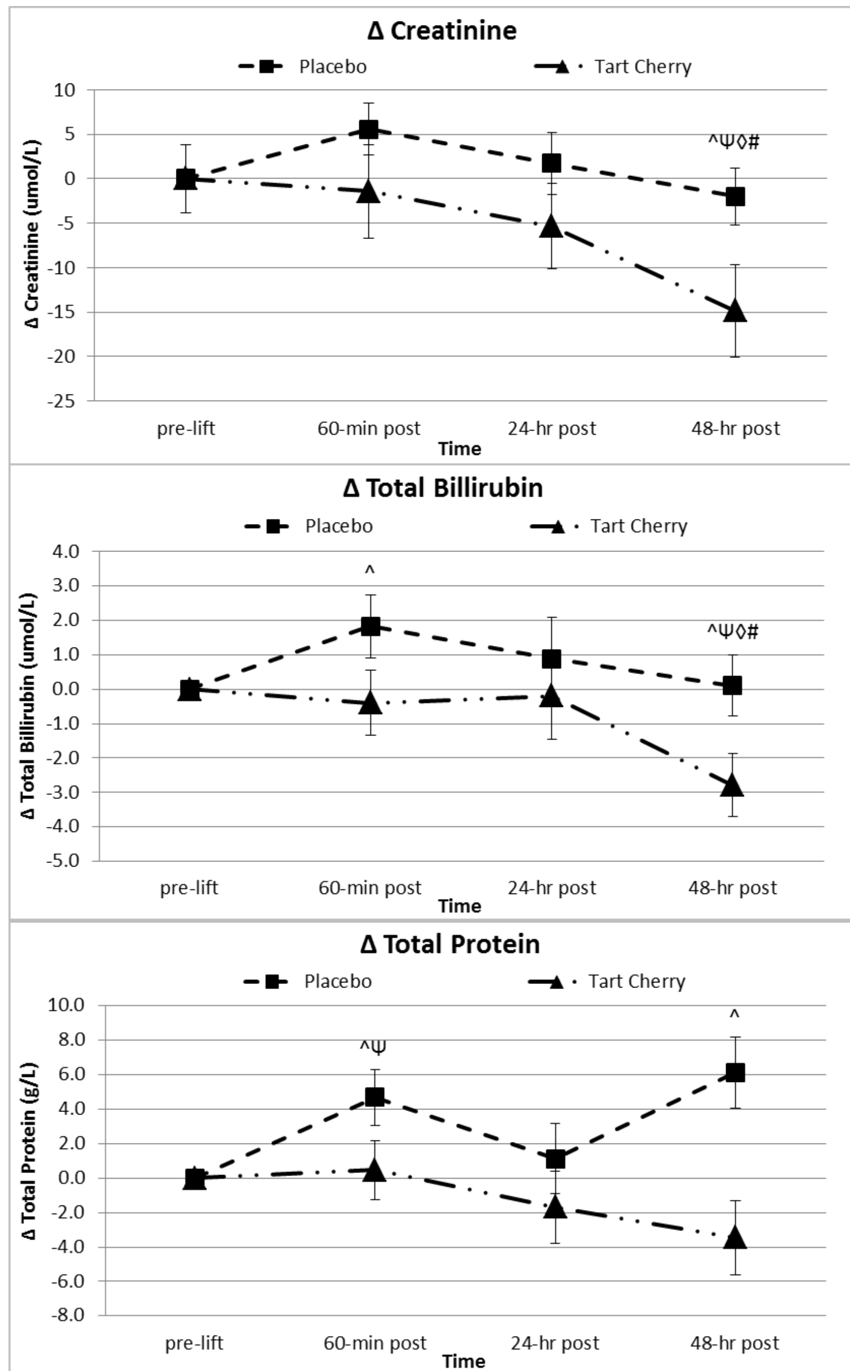

Figure 6. Markers of Protein Catabolism [Resistance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-lift, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

Table 7: Markers of Muscle Catabolism, Secondary Muscle Damage, and Physiological Stress [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
AST (U/L)	P	31.85±9.6	27.47±6.40	30.79±7.88	41.39±13.3	37.67±10.3	33.83±2.19	*G*=0.919	
	TC	37.70±17.6	28.39±7.62	29.53±6.46	40.59±17.5	31.32±11.5	33.51±2.29	*T*=0.003*	T_q=0.759
	Time Mean	34.78±2.93	27.93±1.46†	30.16±1.51$^{\Psi}$	40.99±3.2$^{\Psi\Diamond}$	34.50±2.2$^{\Psi\#}$		$G \times T$=0.316	$G \times T_L$=0.162
ALT (U/L)	P	33.81±18.4	32.21±12.2	34.19±13.6	36.78±14.9	35.80±13.8	34.56±4.19	*G*=0.455	
	TC	31.78±13.2	30.01±19.3	28.32±15.8	31.08±19.5	28.54±17.4	29.94±4.38	*T*=0.529	T_L=0.180
	Time Mean	32.79±3.41	31.11±3.34	31.26±3.07	33.93±3.6$^{\Psi\Diamond}$	32.17±3.27		$G \times T$=0.521	$G \times T_L$=0.266
Total Billirubin (umol/L)	P	8.00±3.67	7.25±3.47	9.08±5.31	8.14±3.82	7.35±3.21	7.96±1.01	*G*=0.395	
	TC	9.65±3.85	9.98±4.95	9.58±4.01	9.79±5.20	7.19±3.21	9.24±1.06	*T*=0.064§	T_q=0.026*
	Time Mean	8.83±0.78	8.61±0.89	9.33±0.99	8.97±0.95	7.27±0.67$^{\dagger\Psi\Diamond\#}$		$G \times T$=0.306	$G \times T_L$=0.125
Urea/BUN (mmol/L)	P	6.59±1.54	6.16±1.74	6.07±1.59	6.48±1.96	5.92±2.33	6.24±0.44	*G*=0.794	
	TC	6.49±1.39	6.75±1.30	6.40±1.33	6.59±1.83	5.83±1.66	6.41±0.46	*T*=0.061§	T_L=0.055§
	Time Mean	6.54±0.31	6.46±0.32	6.24±0.31	6.53±0.40	5.88±0.43$^{\dagger\Psi\#}$		$G \times T$=0.594	$G \times T_q$=0.238
Creatinine (umol/L)	P	96.50±13.2	97.19±19.2	102.76±17.2^	98.91±21.1^	95.20±17.7^$^{\Diamond}$	98.11±4.05	*G*=0.273	
	TC	91.82±11.9	96.84±15.2	95.42±14.3	91.52±11.2	81.99±14.8$^{\dagger\Psi\Diamond\#}$	91.52±4.23	*T*=0.004*	T_q=0.003*
	Time Mean	94.16±2.64	97.02±3.65	99.09±3.33	95.21±3.58	88.60±3.4$^{\dagger\Psi\Diamond\#}$		$G \times T$=0.178	$G \times T_L$=0.030*
BUN/ Creatinine Ratio	P	17.11±4.38	15.97±3.99	14.82±3.66	16.66±5.67	15.50±5.26	16.01±1.08	*G*=0.353	
	TC	17.65±3.76	17.51±3.83	16.82±3.74	17.85±4.35	17.64±3.80	17.50±1.13	*T*=0.214	T_q=0.225
	Time Mean	17.37±4.01	16.71±3.90	15.78±3.75$^{\dagger\Psi}$	17.23±5.00	16.53±4.64		$G \times T$=0.721	$G \times T_L$=0.388

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the response to muscle catabolism, mechanical damage, and physiological stress at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.504). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. AST = Aspartate aminotransferase; ALT= Alanine aminotransferase; BUN = Blood urea nitrogen; CK = Creatine kinase; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Table 7: Markers of Muscle Catabolism, Secondary Muscle Damage, and Physiological Stress [cont.] [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
Uric Acid	P	328±66	317±66	444±136	367±80	349±88	361±20.37	*G*=0.647	
(umol/L)	TC	306±52	310±54	470±117	350±93	302±79	347±21.28	*T*<0.001*	T_q<0.001*
	Time Mean	317±12	314±13	457±27^{†Ψ}	358±18$^{†Ψ◊}$	325±17$^{◊\#}$		*G X T*=0.298	*G X* T_q=0.146
CK	P	468±288	322±243	451±267	967±700	855±981	613±82	*G*=0.487	
(U/L)	TC	843±1156	259±146	355±198	770±470	415±213	529±86	*T*=0.025*	T_q=0.222
	Time Mean	656±172	291±42†	403±49^{Ψ}	869±126$^{Ψ◊}$	635±151^{Ψ}		*G X T*=0.209	*G X* T_L=0.100§
Total	P	78.6±6.11	67.5±7.96$^{\wedge†}$	72.2±6.47^{†Ψ}	68.6±9.45†	73.6±11.11$^{†Ψ\#}$	72.1±1.52	*G*=0.305	
Protein	TC	80.5±4.60	74.1±2.62†	74.5±4.18†	72.4±6.72†	70.6±7.92$^{†Ψ◊}$	74.4±1.59	*T*<0.001*	T_q<0.001*
(mmol/L)	Time Mean	79.6±1.14	70.8±1.26†	73.4±1.15^{†Ψ}	70.5±1.72†	72.1±2.03†		*G X T*=0.091§	*G X* T_q=0.018*

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the response to muscle catabolism, mechanical damage, and physiological stress at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.504). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. AST = Aspartate aminotransferase; ALT= Alanine aminotransferase; BUN = Blood urea nitrogen; CK = Creatine kinase; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

clinical ranges were observed for kidney/liver enzymes [e.g. AST (p=0.16), ALT (p=0.27)] or markers of protein catabolism [bilirubin (p=0.12), BUN:creatinine ratio (p=0.39), uric acid (p=0.15)]. However, further post-hoc analyses revealed TC facilitated post-lift attenuations in bilirubin, AST, and ALT 48-h post-lift compared to P (see figures 6 and 7).

Anabolic/Catabolic Hormone Response Markers

Table 8 shows the serum anabolic and catabolic hormone markers analyzed in response to exercise. The overall MANOVA analyses revealed both non-significant overall Wilks' Lambda time (p=0.29) and overall group changes across time (p=0.46). Cortisol levels tended to change over time (p=0.093). Serum cortisol levels were significantly different between groups over time (p=0.029) and revealed how supplementation caused significant variability (p=0.032) in cortisol changes from pre-lift levels across the recovery period. Serum cortisol levels increased on average 13% over pre-lift values during the recovery in P, but only 8% in TC. The delta post-hoc analysis revealed that TC cortisol levels were not different from pre-lift levels and were significantly lower at 48-h post-lift compared to rising cortisol levels in P (see figure 7).

Markers of Free Radical Production and Oxidative Stress

Table 9 reports the serum markers of free radical production [reactive oxygen species (ROS) and reactive nitrogen species (RNS)] analyzed in response to exercise. The overall MANOVA analysis revealed no significant overall Wilks' Lambda time (p=0.32) interaction and no overall group differences over time (p=0.76). None of the

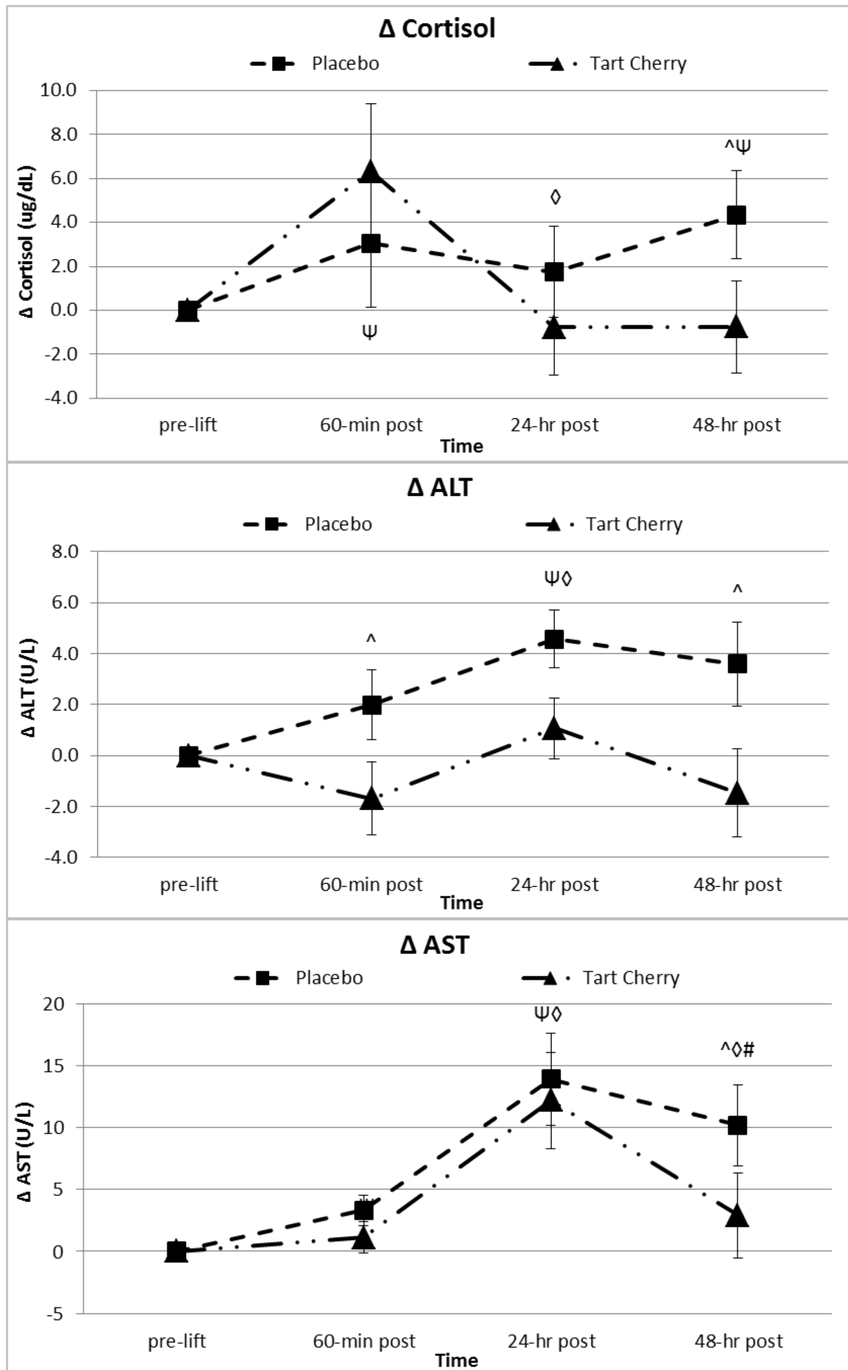

Figure 7. Physiological Stress and Secondary Muscle Damage Indices [Resistance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-lift, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

Table 8: Anabolic/Catabolic Hormone Response [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
Cortisol (ug/dL)	P	28.3 ± 13.1^	23.3 ± 8.8	26.4 ± 7.3	25.1 ± 10.2^	27.7 ± 11.2^	26.2 ± 2.2	*G*=0.167	
	TC	21.5 ± 7.0	20.5 ± 7.9	26.8 ± 12.1†	19.7 ± 5.6◊	19.7 ± 6.8◊	21.6 ± 2.3	*T*=0.093§	T_L=0.611
	Time Mean	24.9 ± 2.2	21.9 ± 1.7	26.6 ± 2.1Ψ	22.4 ± 1.7◊	23.7 ± 1.9		*G X T*=0.170	*G X* T_q=0.029*
Testosterone (ng/mL)	P	9.86 ± 3.46	9.37 ± 3.45	9.25 ± 2.92	10.17 ± 3.55	9.94 ± 3.42	9.72 ± 0.75	*G*=0.025*	
	TC	7.24 ± 2.22	7.17 ± 2.00	6.97 ± 1.95	7.20 ± 2.00	6.91 ± 1.70	7.10 ± 0.79	*T*=0.428	T_q=0.427
	Time Mean	8.55 ± 0.61	8.27 ± 0.60	8.11 ± 0.52	8.68 ± 0.61	8.42 ± 0.57		*G X T*=0.556	*G X* T_L=0.174
Test/Cort Ratio	P	0.037 ± 0.009	0.043 ± 0.014	0.037 ± 0.013	0.045 ± 0.019	0.040 ± 0.018	0.040 ± 0.003	*G*=0.538	
	TC	0.037 ± 0.015	0.040 ± 0.020	0.031 ± 0.015	0.039 ± 0.013	0.040 ± 0.019	0.037 ± 0.004	*T*=0.152	T_L=0.516
	Time Mean	0.037 ± 0.012	0.042 ± 0.017	0.034 ± 0.014	0.042 ± 0.016	0.040 ± 0.018		*G X T*=0.815	*G X* T_q=0.196

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the stress and sex hormone response at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p=0.293) and group x time (p=0.458). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. Test/Cort = Testosterone/Cortisol ratio; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

univariate measures for markers of free radical production, lipid peroxidation, and antioxidant capacity/activity (NT, TBARS, TAS, and SOD) reported main time effects or differences between groups over time.

Inflammatory Response Markers

Table 10 shows the serum inflammatory cytokine and chemokine markers analyzed in response to exercise. The overall MANOVA analysis revealed a significant overall Wilks' Lambda time ($p<0.001$) interaction, but a non-significant overall group x time effect ($p=0.30$). Univariate measures for TNF-α ($p=0.001$), IL-1β ($p=0.030$), IL-6 ($p=0.023$), and IL-8 ($p=0.018$) demonstrated significant changes over time and from baseline measures, peaking 24-h post-lift. No significant differences between groups were observed over time for any of the inflammatory cytokines or chemokines.

Anti-Inflammatory Response Markers

Table 11 presents the serum anti-inflammatory cytokine markers analyzed in response to exercise. The overall MANOVA analysis revealed a significant overall Wilks' Lambda time ($p<0.001$) interaction, but a non-significant overall effect of treatment over time ($p=0.45$). Univariate measures for IL-4 ($p=0.001$) and IL-7 ($p=0.033$) reported significant main time effects with IL-13 levels approaching significance across time ($p=0.055$), peaking 60-min post-lift. No significant group effects over time were reported for any of the anti-inflammatory cytokine markers.

Clinical Markers of Immune-Related Complete Blood Counts

Table 12 displays immune response-related complete blood count markers

Table 9: Markers of Free Radical Production and Oxidative Stress [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
Nitrotyrosine	P	305 ± 267	306 ± 311	297 ± 289	297 ± 330	294 ± 305	300 ± 74	*G*=0.940	
(nM)	TC	303 ± 193	319 ± 254	277 ± 190	275 ± 202	283 ± 203	292 ± 78	*T*=0.280	T_L=0.146
	Time Mean	304 ± 230	312 ± 279	288 ± 241	287 ± 270	289 ± 256$^{\Psi}$		*G X T*=0.613	*G X* T_L=0.483
TBARS	P	7.84 ± 2.69	7.27 ± 2.91	8.60 ± 2.67	8.03 ± 3.34	8.43 ± 3.74	8.03 ± 0.81	*G*=0.913	
(uM)	TC	7.74 ± 4.24	8.24 ± 4.03	7.44 ± 3.84	8.19 ± 3.46	7.91 ± 3.35	7.90 ± 0.84	*T*=0.937	T_L=0.539
	Time Mean	7.79 ± 3.44	7.73 ± 3.44	8.05 ± 3.26	8.10 ± 3.32	8.18 ± 3.49		*G X T*=0.569	*G X* T_L=0.649
TAS	P	2.90 ± 1.34	2.83 ± 1.77	3.02 ± 1.85	2.95 ± 1.47	2.80 ± 1.81	2.90 ± 0.39	*G*=0.752	
(mM)	TC	2.69 ± 1.17	2.39 ± 1.14	2.99 ± 1.07	2.73 ± 1.36	2.81 ± 1.34	2.72 ± 0.41	*T*=0.323	T_q=0.419
	Time Mean	2.80 ± 1.23	2.62 ± 1.48	3.01 ± 1.49	2.84 ± 1.39	2.81 ± 1.57		*G X T*=0.706	*G X* T_L=0.442
SOD	P	0.58 ± 0.07	0.59 ± 0.05	0.59 ± 0.09	0.56 ± 0.08	0.58 ± 0.06	0.58 ± 0.02	*G*=0.668	
(U/mL)	TC	0.55 ± 0.12	0.60 ± 0.09	0.54 ± 0.09	0.57 ± 0.10	0.57 ± 0.11	0.57 ± 0.02	*T*=0.264	T_q=0.827
	Time Mean	0.56 ± 0.10	0.60 ± 0.07†	0.57 ± 0.09	0.57 ± 0.08	0.58 ± 0.09		*G X T*=0.335	*G X* T_L=0.784

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the response to reactive oxygen and nitrogen species production in addition to antioxidant activity at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p=0.321) and group x time (p=0.756). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. TBARS = Thiobarbituric acid reactive substances; TAS = Total antioxidant status; SOD = Superoxide dismutase; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Table 10: Pro-inflammatory Cytokines and Chemokines [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
TNF-α	P	2.82 ± 1.33	3.30 ± 1.59	3.33 ± 1.88	2.98 ± 1.45	2.85 ± 1.41	3.05 ± 0.36	*G*=0.212	
(pg/mL)	TC	2.12 ± 0.92	2.55 ± 1.15	2.61 ± 1.00	2.44 ± 0.82	2.23 ± 0.94	2.39 ± 0.37	*T*=0.003*	T_q=0.001*
	Time Mean	2.47 ± 0.24	2.92 ± 0.29†	2.97 ± 0.32†	2.71 ± 0.25$^{\lozenge}$	2.54 ± 0.25$^{\Psi\lozenge}$		*G X T*=0.873	*G X* T_L=0.649
IFN-γ	P	14.92 ± 31.51	18.91 ± 44.08	18.99 ± 44.51	21.33 ± 51.78	21.56 ± 51.82	19.14 ± 9.41	*G*=0.365	
(pg/mL)	TC	6.19 ± 5.69	6.46 ± 5.01	7.12 ± 5.19	7.11 ± 5.98	5.78 ± 6.02	6.53 ± 9.83	*T*=0.287	T_q=0.136
	Time Mean	10.56 ± 4.83	12.68 ± 6.70	13.06 ± 6.77	14.22 ± 7.87	13.67 ± 7.88$^{\#}$		*G X T*=0.314	*G X* T_L=0.295
IL-1β	P	0.77 ± 0.32	0.84 ± 0.35	0.87 ± 0.39	0.83 ± 0.38	0.83 ± 0.35	0.83 ± 0.10	*G*=0.048*	
(pg/mL)	TC	0.75 ± 0.35	0.75 ± 0.34	0.82 ± 0.26	0.85 ± 0.30	0.82 ± 0.34	0.80 ± 0.10	*T*=0.047*	T_q=0.030*
	Time Mean	0.76 ± 0.07	0.80 ± 0.07†	0.85 ± 0.07†	0.84 ± 0.07	0.82 ± 0.07		*G X T*=0.411	*G X* T_q=0.488
IL-2	P	1.86 ± 1.86	2.00 ± 2.18	1.97 ± 2.16	1.91 ± 2.15	1.87 ± 2.09	1.92 ± 0.71	*G*=0.956	
(pg/mL)	TC	1.70 ± 2.96	1.73 ± 2.73	2.06 ± 2.65	2.26 ± 3.13	2.15 ± 3.03	1.98 ± 0.74	*T*=0.292	T_L=0.214
	Time Mean	1.78 ± 0.51	1.87 ± 0.51	2.02 ± 0.50	2.08 ± 0.56	2.01 ± 0.54		*G X T*=0.230	*G X* T_L=0.163
IL-6	P	1.19 ± 0.95	1.34 ± 1.36	1.61 ± 1.60	1.33 ± 1.38	1.26 ± 1.21	1.35 ± 0.37	*G*=0.724	
(pg/mL)	TC	0.87 ± 1.34	1.09 ± 1.31	1.54 ± 1.38	1.20 ± 1.49	1.07 ± 1.43	1.16 ± 0.39	*T*=0.020*	T_q=0.023*
	Time Mean	1.03 ± 0.24	1.22 ± 0.28	1.57 ± 0.31$^{\dagger\Psi}$	1.27 ± 0.30†	1.17 ± 0.28$^{\lozenge\#}$		*G X T*=0.761	*G X* T_L=0.512
IL-8	P	4.25 ± 3.99	5.07 ± 5.74	5.04 ± 6.16	5.16 ± 6.41	4.94 ± 6.32	4.89 ± 1.23	*G*=0.496	
(pg/mL)	TC	2.95 ± 1.56	3.45 ± 1.75	4.14 ± 1.29	4.02 ± 1.78	3.74 ± 1.91	3.66 ± 1.28	*T*=0.042*	T_q=0.018*
	Time Mean	3.60 ± 0.64	4.26 ± 0.90†	4.59 ± 0.95†	4.59 ± 1.00	4.34 ± 0.99		*G X T*=0.697	*G X* T_L=0.736
IL-12p70	P	2.27 ± 4.13	3.03 ± 6.51	3.05 ± 6.63	3.01 ± 6.42	2.78 ± 5.68	2.83 ± 1.33	*G*=0.577	
(pg/mL)	TC	1.70 ± 2.67	1.76 ± 2.59	1.68 ± 2.15	1.91 ± 2.76	1.66 ± 2.61	1.74 ± 1.39	*T*=0.279	T_q=0.264
	Time Mean	1.99 ± 0.73	2.39 ± 1.05	2.37 ± 1.05	2.46 ± 1.05	2.22 ± 0.94		*G X T*=0.377	*G X* T_L=0.351

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the pro-inflammatory response at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.302). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. TNF-α = Tumor necrosis factor alpha; IFN-γ = Interferon gamma; IL = interleukin; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

analyzed in response to exercise. The overall MANOVA analysis demonstrated significant overall Wilks' Lambda time interaction (p<0.001), but a non-significant overall difference between groups over time (p=0.68). Univariate measures for lymphocytes (p<0.001) and MID (p<0.001) demonstrated significant changes over time and from baseline measures, most depressed 60-min post-lift. WBC (p=0.004) and GRAN (p=0.003) also significantly changed over time, with lowest values 48-h post-lift. MID levels tended to be different between groups over time (p=0.062). Significant group changes over time (p=0.015) and differences in group effects from pre-lift levels over the recovery period (p=0.013) were reported for lymphocytes. Lymphocyte levels decreased on average 23% below pre-lift values during the recovery in P, but only 11% in TC. Subsequent post-hoc analysis showed a significantly greater lymphocyte counts 24-h and 48-h post-lift in TC compared to P, but unlike those supplementing with P, TC lymphocyte counts returned to pre-lift values by the end of the recovery (48-h post-lift). A significant group effect over time was also reported for WBC (p=0.020). WBC decreased on average 8% below pre-lift values during the recovery in P, but only 3% in TC. Post-hoc analysis demonstrated significant WBC differences pre-lift, 24-h, and 48-h post-lift between TC and P that became insignificant once changes were calculated from pre-lift levels.

Table 11: Anti-inflammatory Cytokines [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
IL-4	P	6.03 ± 3.18	7.86 ± 5.06	8.26 ± 5.22	7.44 ± 4.95	7.83 ± 5.10	7.48 ± 1.05	*G*=0.273	
(pg/mL)	TC	4.16 ± 1.91	5.45 ± 2.04	6.38 ± 2.49	6.36 ± 2.45	6.54 ± 3.01	5.78 ± 1.09	*T*=0.001*	T_q=0.001*
	Time Mean	5.10 ± 0.55	6.65 ± 0.82†	7.32 ± 0.87†	6.90 ± 0.83†◊	7.19 ± 0.88†		*G X T*=0.421	*G X* T_L=0.405
IL-5	P	0.69 ± 0.37	0.70 ± 0.41	0.70 ± 0.46	0.64 ± 0.37	0.65 ± 0.40	0.68 ± 0.11	*G*=0.749	
(pg/mL)	TC	0.75 ± 0.43	0.72 ± 0.40	0.71 ± 0.37	0.77 ± 0.43	0.70 ± 0.42	0.73 ± 0.12	*T*=0.716	T_L=0.325
	Time Mean	0.72 ± 0.08	0.71 ± 0.09	0.70 ± 0.09	0.71 ± 0.08	0.68 ± 0.09		*G X T*=0.438	*G X* T_L=0.582
IL-7	P	4.73 ± 2.19	5.41 ± 2.49	5.94 ± 3.71	5.52 ± 2.75	5.46 ± 2.57	5.41 ± 0.63	*G*=0.414	
(pg/mL)	TC	4.15 ± 1.86	4.45 ± 2.00	5.31 ± 2.18	4.91 ± 1.61	4.47 ± 1.54	4.66 ± 0.65	*T*=0.041*	T_q=0.033*
	Time Mean	4.44 ± 0.43	4.93 ± 0.48†	5.62 ± 0.64†	5.21 ± 0.48†	4.97 ± 0.45†		*G X T*=0.843	*G X* T_L=0.757
IL-10	P	4.52 ± 3.85	3.69 ± 1.82	4.21 ± 1.92	3.48 ± 1.70	3.45 ± 1.74	3.87 ± 0.56	*G*=0.869	
(pg/mL)	TC	2.77 ± 1.74	3.49 ± 2.03	6.02 ± 5.70	3.33 ± 2.54	3.07 ± 2.54	3.74 ± 0.59	*T*=0.103§	T_q=0.157
	Time Mean	3.65 ± 0.63	3.59 ± 0.40	5.12 ± 0.87Ψ	3.41 ± 0.45	3.26 ± 0.45		*G X T*=0.182	*G X* T_q=0.120
IL-13	P	3.30 ± 2.89	3.33 ± 3.30	3.40 ± 3.48	3.24 ± 3.64	3.27 ± 3.56	3.31 ± 0.78	*G*=0.449	
(pg/mL)	TC	1.96 ± 1.74	2.26 ± 1.66	2.75 ± 2.09	2.78 ± 2.18	2.45 ± 2.34	2.44 ± 0.81	*T*=0.393	T_q=0.055§
	Time Mean	2.63 ± 0.50	2.80 ± 0.55	3.08 ± 0.61	3.01 ± 0.63	2.86 ± 0.64		*G X T*=0.402	*G X* T_q=0.133

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the anti-inflammatory response at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.447). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. IL = interleukin; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Table 12: Markers of Immune-Related Complete Blood Counts [Resistance]

Variable	Group	Baseline	Pre-Lift	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)
LYMPH	P	1.93 ± 0.54	2.21 ± 0.69	1.45 ± 0.43 $^{\dagger\Psi}$	1.86 ± 0.71^ $^{\Psi\Diamond}$	1.78 ± 0.48^ $^{\Psi\Diamond}$	1.85 ± 0.20	*G*=0.311	
(K/uL)	TC	2.09 ± 0.86	2.36 ± 1.05 †	1.49 ± 0.58 $^{\dagger\Psi}$	2.62 ± 1.51 $^{\dagger\Psi\Diamond}$	2.15 ± 0.78 $^{\Diamond\#}$	2.14 ± 0.21	*T*<0.001*	T_q=0.136
	Time Mean	2.01 ± 0.15	2.28 ± 0.18 †	1.47 ± 0.11 $^{\dagger\Psi}$	2.24 ± 0.24 $^{\Diamond}$	1.97 ± 0.13 $^{\Psi\Diamond}$		*G X T*=0.143	$G\ X\ T_L$=0.015*
WBC	P	5.88 ± 1.23	6.61 ± 2.21^	6.38 ± 1.45	6.16 ± 1.62^	5.75 ± 1.61^	6.16 ± 0.40	*G*=0.337	
(K/uL)	TC	5.54 ± 1.25	7.18 ± 2.03 †	6.98 ± 2.04 †	7.40 ± 2.17 †	6.55 ± 1.23 $^{\dagger\#}$	6.73 ± 0.42	*T*=0.004*	T_q=0.004*
	Time Mean	5.71 ± 0.26	6.90 ± 0.44 †	6.68 ± 0.37 †	6.78 ± 0.40 †	6.15 ± 0.30 $^{\Psi}$		*G X T*=0.207	$G\ X\ T_L$=0.020*
MID	P	0.43 ± 0.12	0.64 ± 0.19	0.43 ± 0.14	0.53 ± 0.13	0.48 ± 0.13	0.50 ± 0.03	*G*=0.866	
(K/uL)	TC	0.42 ± 0.10	0.61 ± 0.24	0.38 ± 0.10	0.60 ± 0.19	0.55 ± 0.16	0.51 ± 0.03	*T*<0.001*	T_L=0.100§
	Time Mean	0.43 ± 0.02	0.63 ± 0.05 †	0.41 ± 0.03 $^{\Psi}$	0.56 ± 0.03 $^{\dagger\Diamond}$	0.51 ± 0.03 $^{\dagger\Psi\Diamond}$		*G X T*=0.324	$G\ X\ T_L$=0.062§
GRAN	P	3.50 ± 0.97	3.76 ± 1.47	4.51 ± 1.20	3.78 ± 1.33	3.48 ± 1.32	3.80 ± 0.33	*G*=0.577	
(K/uL)	TC	3.04 ± 0.48	4.22 ± 1.77	5.11 ± 2.35	4.17 ± 1.61	3.84 ± 0.98	4.08 ± 0.35	*T*<0.001*	T_q=0.002*
	Time Mean	3.27 ± 0.16	3.99 ± 0.34 †	4.81 ± 0.38 $^{\dagger\Psi}$	3.97 ± 0.31 $^{\dagger\Diamond}$	3.66 ± 0.03 $^{\Diamond}$		*G X T*=0.332	$G\ X\ T_L$=0.119
GM-CSF	P	8.12 ± 8.23	8.18 ± 8.33	7.87 ± 7.38	7.54 ± 7.67	7.39 ± 7.49	7.82 ± 2.71	*G*=0.512	
(pg/mL)	TC	10.37 ± 11.40	10.51 ± 10.83	10.52 ± 10.48	10.67 ± 11.19	10.09 ± 10.89	10.43 ± 2.83	*T*=0.446	T_L=0.277
	Time Mean	9.24 ± 2.06	9.34 ± 2.00	9.20 ± 1.88	9.10 ± 1.99	8.74 ± 1.93		*G X T*=0.624	$G\ X\ T_L$=0.450

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents immune cellular response markers at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.684). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. LYMPH = Lymphocytes; WBC = White blood cell; MID = Mid-range absolute count; GRAN = Granulocyte absolute count; GM-CSF = Granulocyte-macrophage colony-stimulating factor; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Tart Cherry Endurance

Subject Baseline Characteristics

A total of 27 healthy, endurance trained or triathlete men (n=18) and women (n=9) completed the study protocol. Participants were 21.8±3.9 years, 67.4±11.8 kg, 15.0±6.0% body fat, and 51.2±11.4 kg fat free mass. Participant demographic data are presented in Table 13. One-way ANOVA revealed no significant differences ($p>0.05$) in baseline demographic or anthropometric markers. Specifically, no significant differences in resting heart rate ($p=0.70$) were reported across groups, hence the groups were generally well matched and endurance trained. Observed differences can likely be attributed to the nutritional intervention.

Nutritional Intake and Compliance

Table 14 lists relevant nutrition components analyzed in the 4-d dietary recall completed by all subjects during the first 7-d of supplementation. According to the data listed in Table 14, P group tended to consume a smaller amount of average daily calories compared to the TC group (31.0 kcal/kg vs. 37.4 kcal/kg, $p=0.094$). This differential is likely due dropped subjects (see Figure 3) causing a greater proportion of females in the placebo group (n_f=3/11, 27.3%) versus the powdered tart cherry group (n_f=6/16, 37.5%). Stratifying the statistical dietary analysis by gender within each group, average daily calorie ($p=0.441$) and dietary carbohydrate ($p=0.644$) consumption was the same across groups. No other statistically significant interactions were observed across groups with respect to dietary intake.

Table 13: Demographics by Study Group [Endurance]

Variable	Group	Mean	Group (SEM)	p-value
N	P	16	n/a	n/a
	TC	11	n/a	
	Total	27	n/a	
Age (yrs)	P	22.44 ± 4.86	1.214	0.305
	TC	20.82 ± 1.89	0.569	
	Total	21.78 ± 3.95	0.761	
Height (cm)	P	173 ± 11.43	2.851	0.592
	TC	175 ± 8.59	2.589	
	Total	174 ± 10.25	1.972	
Weight (kg)	P	65.48 ± 12.07	3.018	0.317
	TC	70.17 ± 11.25	3.392	
	Total	67.39 ± 11.76	2.263	
Baseline HR (bpm)	P	58.50 ± 9.02	2.255	0.703
	TC	59.64 ± 4.46	1.343	
	Total	58.96 ± 58.96	1.426	
BMD (g/cm^2)	P	1.04 ± 0.11	0.028	0.458
	TC	1.08 ± 0.13	0.038	
	Total	1.06 ± 0.12	0.023	
FFM (kg)	P	48.67 ± 11.32	2.830	0.171
	TC	54.85 ± 11.01	3.319	
	Total	51.19 ± 11.41	2.195	
FM (kg)	P	9.81 ± 3.20	0.801	0.085§
	TC	7.76 ± 2.44	0.735	
	Total	2.44 ± 3.04	0.585	
Body Fat (%)	P	16.87 ± 6.40	1.599	0.051§
	TC	12.31 ± 4.42	1.333	
	Total	15.01 ± 6.03	1.160	

Mean data expressed as means ± SD. Data represents general study population demographics and anthropometric measures. One-way ANOVA p-levels listed for each variable: * represents p<0.05 difference between groups, § represents p<0.10 difference between groups. HR = heart rate; BMD = bone mineral density; LM = lean mass; FFM = free-fat mass; FM = fat mass.

Half-Marathon Performance Measures

Table 15 presents half-marathon split and finish times in addition to projected versus actual average race paces as records of endurance performance. There was no difference in projected race finish times between groups (p=0.304). Subjects in the TC group had faster half-marathon split (p=0.002) and race finish times (p=0.001)

Table 14: Relative Dietary Analysis by Study Group [Endurance]

Variable	Group	Mean	Group (SEM)	p-value
Average Daily Caloric Consumption (kcal/kg)	P	30.89 ± 8.75	2.19	0.094§
	TC	37.71 ± 11.65	3.51	
	Total	33.67 ± 10.40	2.00	
Dietary Protein (g/kg)	P	1.29 ± 0.56	0.14	0.146
	TC	1.62 ± 0.58	0.17	
	Total	1.42 ± 0.58	0.11	
Dietary Carbohydrates (g/kg)	P	3.54 ± 1.50	0.37	0.138
	TC	4.57 ± 2.00	0.60	
	Total	3.96 ± 1.76	0.34	
Dietary Fat (g/kg)	P	1.24 ± 0.49	0.12	0.886
	TC	1.27 ± 0.72	0.22	
	Total	1.25 ± 0.58	0.11	
Dietary Beta-Carotene (mcg/kg)	P	38.01 ± 71.15	17.79	0.611
	TC	54.22 ± 92.29	27.83	
	Total	44.62 ± 79.13	15.23	
Dietary Vitamin C [Ascorbic Acid] (mg/kg)	P	0.92 ± 0.69	0.17	0.277
	TC	1.46 ± 1.78	0.54	
	Total	1.14 ± 1.25	0.24	
Dietary Vitamin E [Alpha-Tocopherol] (mg/kg)	P	0.099 ± 0.095	0.024	0.853
	TC	0.106 ± 0.107	0.032	
	Total	0.102 ± 0.098	0.019	

Mean data expressed as means ± SD. Data represents nutritional analysis from subject 4-d dietary records accounting for subject body mass as a computation of relative dietary components. One-way ANOVA p-levels listed for each variable: * represents p<0.05 difference between groups, § represents p<0.10 difference between groups.

corresponding to a quicker overall race pace compared to P. There was an increase in actual race pace over projected race pace across both groups ($p<0.001$), but the difference between projected versus actual race pace tended to be smaller ($p=0.091$) in TC compared to P. Due to the significant difference in race performance and thus running intensity, half-marathon finish time was used as a covariate in subsequent

ANCOVA analyses to determine if other statistical outcomes were attributed to running intensity or to supplementation.

Table 15: Running Performance by Study Group [Endurance]

Variable	Group	Mean	Group (SEM)	p-value
½ Marathon Split Time (min)	P	54.30 ± 4.18	1.045	0.002*
	TC	49.03 ± 3.65	1.099	
	Total	52.15 ± 4.71	0.906	
½ Marathon Finish Time (min)	P	118 ± 9.72	2.429	0.001*
	TC	103 ± 9.28	2.798	
	Total	112 ± 11.86	2.283	
½ Marathon Projected Race Pace (min/km)	P	12.00 ± 1.28	0.338	0.304
	TC	11.45 ± 1.45	0.407	
	Total	11.77 ± 1.35	0.264	
½ Marathon Actual Race Pace (min/km)	P	14.48 ± 1.19	0.293	0.002*
	TC	12.70 ± 1.14	0.354	
	Total	13.76 ± 1.45	0.230	

Mean data expressed as means ± SD. Data represents ½ marathon race performance. Data represents the half-marathon performance measures. Half-marathon projected race pace figures were calculated based upon subjects' self-reported previous endurance running race performances. The overall MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.091). Univariate ANOVA p-levels from the MANOVA analysis are presented for both pacing variables. One-way ANOVA p-levels listed for each timing variable: * represents p<0.05 difference between groups, § represents p<0.10 difference between groups.

Markers of Mechanical Damage and Physiological Stress

Table 16 presents the serum mechanical damage and physiological stress markers tested in the standard clinical safety panel. The overall MANOVA analysis revealed a significant Wilks' Lambda time (p<0.001) effect, but a non-significant difference between groups over time (p=0.70). All of the univariate measures for markers of

muscle damage and physiological stress reported significant changes over time. Univariate measures for serum creatinine (p=0.087), urea/BUN (p=0.095), and total protein (p=0.066) approached statistical significance in differences between groups over time. Serum creatinine and urea/BUN makers increased on average 19% and 21%, respectively, over pre-run values during the recovery in P, but only 6% and 3% in TC. Serum total protein content increased on average 4% over pre-run values during the recovery in P, but actually decreased 3% below pre-lift in TC. Accounting for running intensity differences, ANCOVA revealed that serum creatinine, urea/BUN, and total protein all maintained significant group differences over time. Analyzing the change from pre-run levels demonstrated significant (or approaching significant trends) changes across groups and group differences over time for creatinine (p=0.047, group p=0.007), urea/BUN (p=0.048, group p=0.004), and total protein (p=0.081, group p=0.060) that were further supported by ANCOVA analyses accounting for running intensity. Subsequent post-hoc analysis indicated a significantly attenuated serum creatinine levels 60-min post-run in TC and a moderated urea/BUN response in TC compared to P 24-h post-run (see figure 8). The total protein response never increased above pre-run levels over the 48-h recovery in TC compared to significant elevations in P markers of total protein 60-min and 48-h post-run (see figure 9).

Anabolic/Catabolic Hormone Response Markers

Table 17 shows the serum anabolic and catabolic hormone markers analyzed in response to exercise. The overall MANOVA analysis revealed a significant Wilks'

Table 16: Markers of Muscle Catabolism, Secondary Muscle Damage, and Physiological Stress [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
AST (U/L)	P	32.69 ± 33.67	26.62 ± 14.97	37.20 ± 17.36	50.52 ± 22.96	43.33 ± 16.68	38.07 ± 3.98	*G*=0.911		*G*=0.402
	TC	29.46 ± 10.54	26.30 ± 7.48	36.96 ± 9.68	49.97 ± 31.12	44.14 ± 24.60	37.37 ± 4.80	*T*=0.002*	T_L=0.005*	T_q=0.593
	Time Mean	31.08 ± 5.27	26.46 ± 2.45	37.08 ± 2.89$^{\dagger\Psi}$	50.25 ± 5.20$^{\dagger\Psi\lozenge}$	43.74 ± 3.96$^{\dagger\Psi\#}$		*G X T*=0.859	*G X* T_q=0.740	*G X* T_L=0.707
ALT (U/L)	P	22.09 ± 13.55	20.32 ± 7.15	23.65 ± 8.04	26.42 ± 7.36	28.53 ± 8.02	24.20 ± 2.15	*G*=0.576		*G*=0.057§
	TC	23.06 ± 8.22	23.13 ± 10.39	26.36 ± 10.22	27.94 ± 14.22	30.07 ± 14.80	26.11 ± 2.59	*T*=0.008*	T_L=0.006*	T_q=0.677
	Time Mean	22.57 ± 2.29	21.73 ± 1.68	25.01 ± 1.76$^{\Psi}$	27.18 ± 2.09$^{\Psi\lozenge}$	29.30 ± 2.20$^{\dagger\Psi\lozenge\#}$		*G X T*=0.842	*G X* T_q=0.603	*G X* T_L=0.869
Total Billirubin (umol/L)	P	9.01 ± 2.87	8.15 ± 3.03	13.03 ± 4.68	8.44 ± 4.06	7.65 ± 3.45	9.25 ± 0.76	*G*=0.756		*G*=0.614
	TC	8.71 ± 4.64	7.60 ± 3.75	11.65 ± 4.50	8.99 ± 4.22	7.46 ± 2.75	8.88 ± 0.91	*T*<0.001*	T_q=0.001*	T_q=0.484
	Time Mean	8.86 ± 0.72	7.88 ± 0.65	12.34 ± 0.90$^{\dagger\Psi}$	8.71 ± 0.81$^{\lozenge}$	7.55 ± 0.62$^{\lozenge}$		*G X T*=0.699	*G X* T_L=0.694	*G X* T_q=0.591
Urea/ BUN (mmol/L)	P	4.75 ± 1.08	5.45 ± 1.36	6.36 ± 1.14	7.13 ± 1.15	6.33 ± 1.44	6.00 ± 0.21	*G*=0.857		*G*=0.426
	TC	5.11 ± 0.69	6.02 ± 1.17	6.16 ± 1.01	6.40 ± 1.44	6.03 ± 1.58	5.94 ± 0.26	*T*<0.001*	T_L<0.001*	T_L=0.026*
	Time Mean	4.93 ± 0.19	5.74 ± 0.25†	6.26 ± 0.21$^{\dagger\Psi}$	6.77 ± 0.25$^{\dagger\Psi}$	6.18 ± 0.29$^{\dagger\#}$		*G X T*=0.144	*G X* T_L=0.095§	*G X* T_L=0.014*
Creatinine (umol/L)	P	71.71 ± 15.07	74.29 ± 11.54	106.56 ± 15.45$^{\dagger\Psi}$	79.85 ± 10.88$^{\dagger\lozenge}$	78.20 ± 11.17†	82.12 ± 3.12	*G*=0.651		*G*=0.522
	TC	77.20 ± 15.93	82.29 ± 13.96	100.44 ± 25.52$^{\dagger\Psi}$	81.54 ± 15.08$^{\lozenge}$	80.34 ± 12.72	84.36 ± 3.77	*T*<0.001*	T_q<0.001*	T_L=0.007*
	Time Mean	74.45 ± 3.02	78.29 ± 2.46	103.50 ± 3.94$^{\dagger\Psi}$	80.70 ± 2.49$^{\dagger\lozenge}$	79.27 ± 2.31$^{\lozenge}$		*G X T*=0.087§	*G X* T_L=0.246	*G X* T_L=0.010*

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the response to muscle catabolism, mechanical damage, and physiological stress at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.504). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. AST = Aspartate aminotransferase; ALT= Alanine aminotransferase; BUN = Blood urea nitrogen; CK = Creatine kinase; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Table 16: Markers of Muscle Catabolism, Secondary Muscle Damage, and Physiological Stress [cont.] [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value(WSC)
BUN/ Creatinine Ratio	P	16.60 ± 3.05	18.58 ± 5.58	15.22 ± 4.38	22.49 ± 4.61	20.36 ± 5.29	18.65 ± 0.90	*G*=0.589		*G*=0.329
	TC	16.97 ± 3.87	18.33 ± 3.50	15.80 ± 3.53	19.50 ± 3.61	18.79 ± 5.26	17.88 ± 1.09	*T*<0.001*	T_L=0.001*	T_q=0.240
	Time Mean	16.75 ± 3.34	18.48 ± 4.77	15.46 ± 3.99$^{\Psi}$	21.27 ± 4.41$^{\dagger\Psi\Diamond}$	19.72 ± 5.23$^{\dagger\Diamond\#}$		*G X T*=0.158	*G X* T_L=0.140	*G X* T_L=0.103§
Uric Acid (umol/L)	P	271 ± 46	292 ± 44	373 ± 48	321 ± 48	308 ± 47	313 ± 11	*G*=0.789		*G*=0.724
	TC	290 ± 50	308 ± 52	364 ± 64	326 ± 82	302 ± 65	318 ± 14	*T*<0.001*	T_q<0.001*	T_L=0.014*
	Time Mean	280 ± 9	300 ± 9†	369 ± 11$^{\dagger\Psi}$	324 ± 13$^{\dagger\Psi\Diamond}$	305 ± 11$^{\dagger\Diamond\#}$		*G X T*=0.444	*G X* T_L=0.188	*G X* T_L=0.015*
CK (U/L)	P	606 ± 1696	276 ± 510	532 ± 627	907 ± 683	593 ± 525	583 ± 144	*G*=0.626		*G*=0.806
	TC	298 ± 317	228 ± 191	474 ± 253	870 ± 771	490 ± 395	472 ± 173	*T*=0.036*	T_L=0.139	T_q=0.836
	Time Mean	452 ± 260	252 ± 81	503 ± 100$^{\Psi}$	889 ± 141$^{\Psi\Diamond}$	541 ± 93$^{\Psi\#}$		*G X T*=0.680	*G X* T_q=0.416	*G X* T_q=0.599
Total Protein (mmol/L)	P	67.51 ± 8.56	72.93 ± 5.41†	76.78 ± 4.95†	70.77 ± 5.35$^{\Diamond}$	80.21 ± 6.48$^{\dagger\Psi\#}$	73.64 ± 0.87	*G*=0.746		*G*=0.846
	TC	68.70 ± 8.06	76.28 ± 4.78†	74.94 ± 8.85†	67.83 ± 4.52$^{\Diamond}$	78.20 ± 6.84$^{\dagger\#}$	73.19 ± 1.05	*T*<0.001*	T_L<0.001*	T_L=0.008*
	Time Mean	68.11 ± 1.64	74.61 ± 1.01†	75.86 ± 1.33†	69.30 ± 0.99$^{\Psi\Diamond}$	79.20 ± 1.30$^{\dagger\Psi\Diamond\#}$		*G X T*=0.316	*G X* T_L=0.066§	*G X* T_L=0.004*

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the response to muscle catabolism, mechanical damage, and physiological stress at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.504). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. AST = Aspartate aminotransferase; ALT= Alanine aminotransferase; BUN = Blood urea nitrogen; CK = Creatine kinase; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

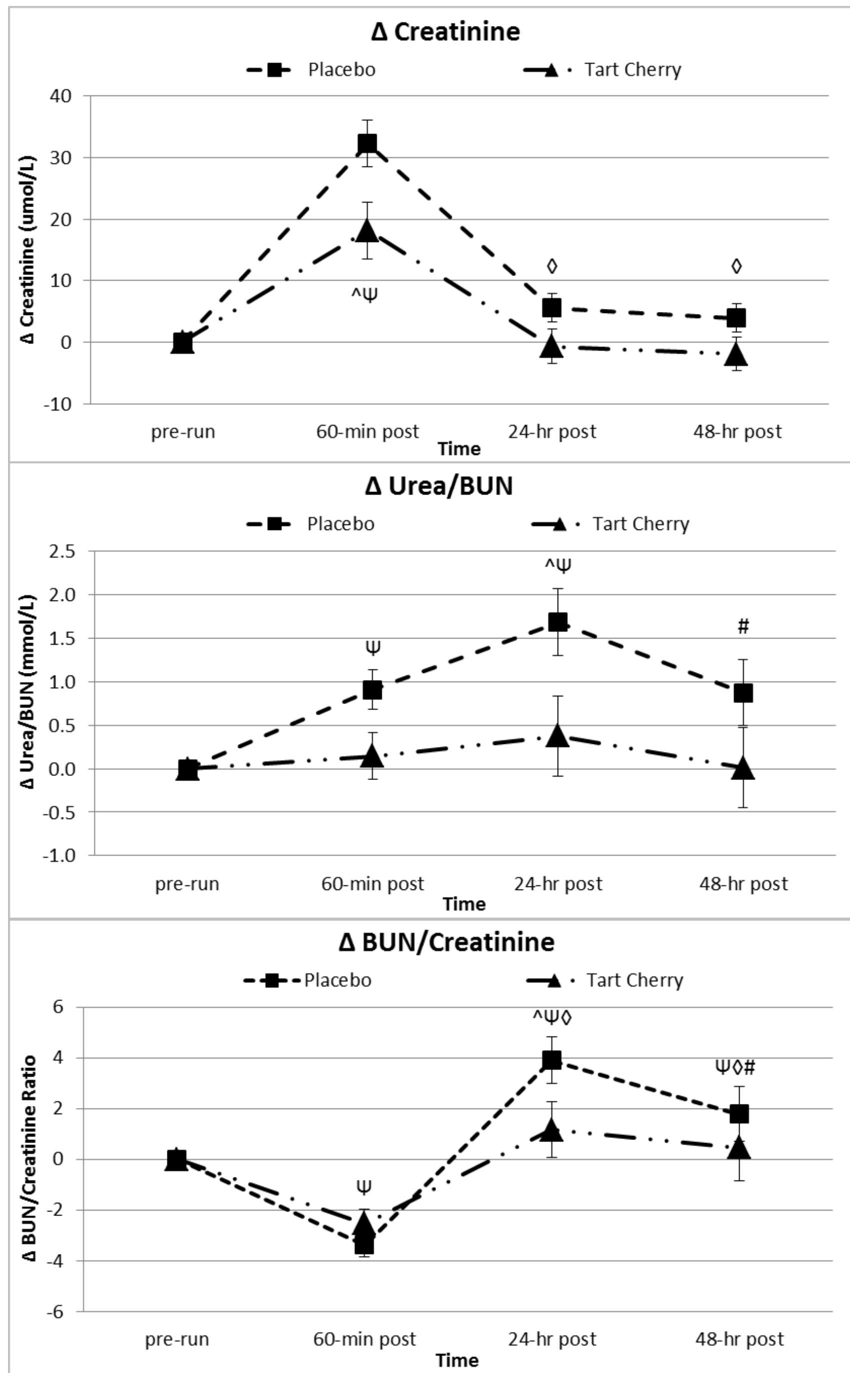

Figure 8. Secondary Indices of Muscle Damage and Protein Catabolism [Endurance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-lift, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

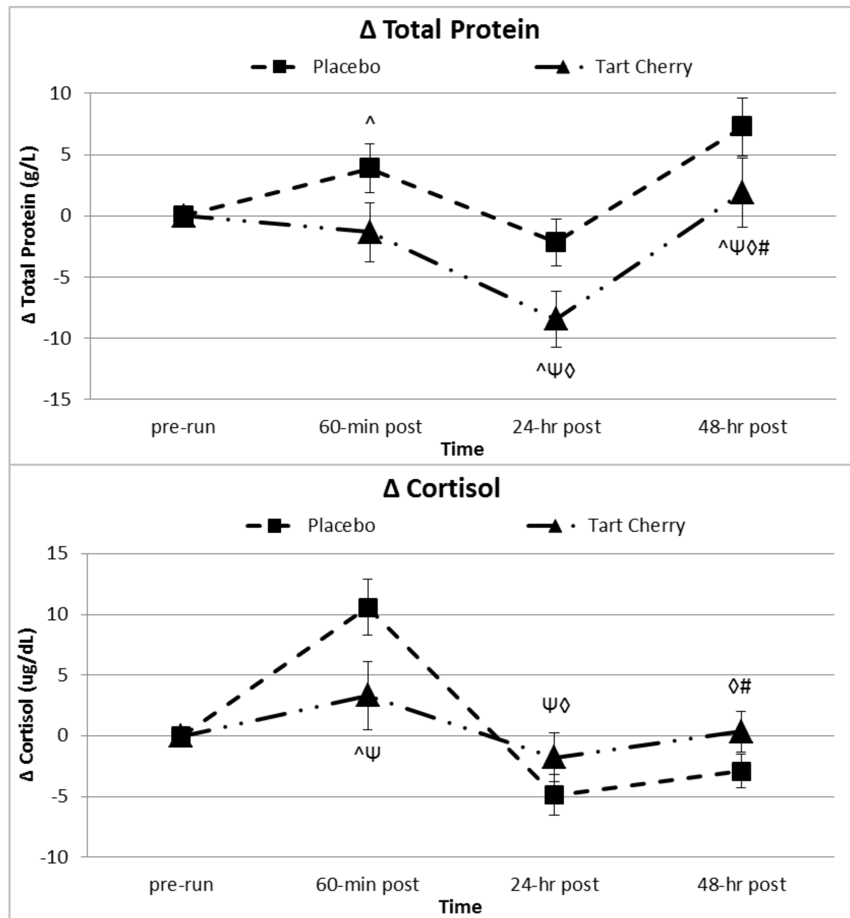

Figure 9. Markers of Protein Catabolism and Physiological Stress [Endurance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-lift, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

Lambda time ($p<0.001$) interaction while group measures tended to be different over time ($p=0.10$). Univariate measures for anabolic/catabolic hormones demonstrated significant changes over time and from baseline measures, peaking (elevated or depressed) 60-min post-run. Significant group differences over time and group changes from pre-run over time were reported for serum cortisol ($p=0.012$, delta $p=0.016$). Serum cortisol levels 60-min post-run increased 44% over pre-run values in P, but only

15% in TC. Subsequent post-hoc analysis indicated a significantly attenuated serum cortisol levels in TC compared to P measures 60-min and 24-h post-run (see figure 9). These results were further supported by ANCOVA analyses accounting for differences in running intensity.

Markers of Free Radical Production and Oxidative Stress

Table 18 shows the markers of free radical production and oxidative stress in response to the aerobic exercise. The overall MANOVA analysis revealed no significant Wilks' Lambda time ($p=0.70$) interaction and no effect among groups over time ($p=0.90$). None of the univariate measures for free radical production or oxidative stress demonstrated significant changes over time. Serum TAS levels tended to be different between groups over time ($p=0.089$), which was attributed to supplement differences after using an ANCOVA analysis to account for running intensity variation between study groups. Serum TAS levels decreased from pre-run 1-8% in P over the 48-h recovery, but increased 15-31% over pre-run levels in TC. A significant difference in delta changes from pre-run levels over the post-run recovery was also reported for serum TAS ($p=0.046$) within the MANOVA univariate analysis. Post-hoc analysis demonstrated a linear increase in serum TAS activity from pre-run levels in TC that was statistically different from P and pre-run values at 48-h of recovery (see Figure 10).

Inflammatory Response Markers

Table 19 shows the serum inflammatory cytokine and chemokine markers analyzed in response to exercise. The overall MANOVA analysis revealed a significant

Wilks' Lambda time ($p<0.001$) effect, but non-significant differences between groups over time ($p=0.83$). Univariate measures for all inflammatory markers demonstrated significant changes over time (excluding IFN-γ), peaking 60-min post-run. IL-6 levels tended to be different between groups over time ($p=0.053$) coupled with a significant difference solely across groups ($p=0.017$). Accounting for running intensity differences using an ANCOVA analysis, both IL-2 ($p=0.089$) and IL-6 ($p=0.064$) measures tended to be different between groups over time. Serum IL-2 levels on average increased 0.2% from pre-run levels over the post-run recovery in P, but decreased 28% from pre-run in TC. Further, serum IL-6 levels increased 64% on average from pre-run in P, but only 17% in TC. The IL-2 group ($p=0.069$) and group over time ($p=0.079$) differences from

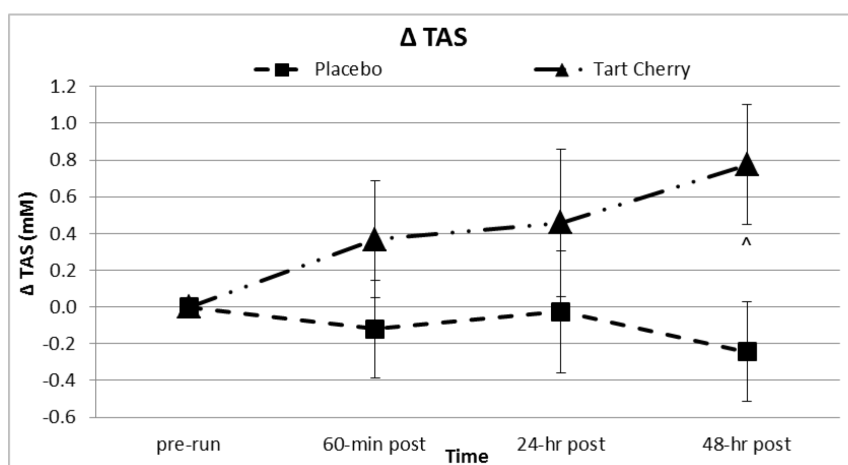

Figure 10. Changes in Antioxidant Activity with Supplementation and Endurance Exercise [Endurance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-run, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

Table 17: Anabolic/Catabolic Hormone Response [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
Cortisol (ug/dL)	P	20.92 ± 7.21	24.04 ± 5.16	34.63 ± 10.14^$^{\dagger\Psi}$	19.17 ± 4.87$^{\Psi\Diamond}$	21.14 ± 5.83$^{\Diamond}$	23.98 ± 1.23	G=0.408		G=0.868
	TC	21.34 ± 6.68	22.14 ± 7.35	25.48 ± 7.45	20.36 ± 5.93$^{\Diamond}$	22.50 ± 4.77	22.36 ± 1.48	T<0.001*	T_q<0.001*	T_L=0.259
	Time Mean	21.13 ± 1.37	23.09 ± 1.20	30.06 ± 1.80$^{\dagger\Psi}$	19.76 ± 1.04$^{\Psi\Diamond}$	21.82 ± 1.06$^{\Diamond\#}$		$G \times T$=0.005*	$G \times T_q$=0.012*	$G \times T_q$=0.030*
Testost. (ng/mL)	P	7.22 ± 3.90	6.77 ± 3.55	6.34 ± 3.55	6.48 ± 3.32	6.74 ± 3.41	6.71 ± 0.88	G=0.745		G=0.497
	TC	6.65 ± 4.24	6.52 ± 3.89	5.59 ± 3.48	6.21 ± 3.75	6.31 ± 3.69	6.26 ± 1.06	T=0.058§	T_q=0.042*	T_q=0.026*
	Time Mean	6.94 ± 0.79	6.64 ± 0.72	5.96 ± 0.69$^{\dagger\Psi}$	6.34 ± 0.69	6.53 ± 0.69		$G \times T$=0.848	$G \times T_L$=0.881	$G \times T_L$=0.171
Test/Cort Ratio	P	0.037 ± 0.026	0.030 ± 0.018	0.019 ± 0.010	0.035 ± 0.024	0.034 ± 0.020	0.031 ± 0.005	G=0.874		G=0.546
	TC	0.035 ± 0.023	0.035 ± 0.023	0.026 ± 0.023	0.034 ± 0.024	0.030 ± 0.021	0.032 ± 0.006	T=0.001*	T_q=0.009*	T_q=0.588
	Time Mean	0.036 ± 0.024	0.032 ± 0.020	0.022 ± 0.016$^{\dagger\Psi}$	0.035 ± 0.023$^{\Diamond}$	0.032 ± 0.020$^{\Diamond}$		$G \times T$=0.327	$G \times T_q$=0.101§	$G \times T_q$=0.290

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the stress and sex hormone response at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.102). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-run, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. Testost. = Testosterone; Cort/Test = Cortisol/Testosterone ratio; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Table 18: Markers of Free Radical Production and Oxidative Stress [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
Nitrotyrosine	P	279 ± 305	214 ± 164	231 ± 180	193 ± 139	198 ± 156	223 ± 71	G=0.493		G=0.852
(nM)	TC	305 ± 425	284 ± 382	319 ± 436	260 ± 352	302 ± 435	294 ± 85	T=0.177	T_L=0.183	T_q=0.667
	Time Mean	292 ± 70	249 ± 53	275 ± 60$^{\Psi}$	227 ± 48$^{\Psi\Diamond}$	250 ± 58$^{\Diamond}$		$G X T$=0.699	$G X T_L$=0.619	$G X T_L$=0.597
TBARS	P	8.24 ± 4.62	7.59 ± 2.54	7.01 ± 4.24	7.35 ± 3.52	7.73 ± 3.39	7.59 ± 0.71	G=0.484		G=0.840
(uM)	TC	8.34 ± 4.06	7.94 ± 4.08	7.91 ± 3.46	8.93 ± 4.52	8.79 ± 4.09	8.38 ± 0.86	T=0.690	T_q=0.332	T_q=0.462
	Time Mean	8.29 ± 0.86	7.77 ± 0.64	7.46 ± 0.77	8.14 ± 0.77	8.26 ± 0.72		$G X T$=0.783	$G X T_L$=0.547	$G X T_L$=0.520
TAS	P	3.13 ± 0.85	3.20 ± 0.88^	3.08 ± 0.89	3.18 ± 1.08	2.96 ± 0.95	3.11 ± 0.17	G=0.476		G=0.381
(mM)	TC	2.99 ± 0.84	2.50 ± 0.97	2.87 ± 1.07	2.96 ± 1.26	3.27 ± 0.87$^{\Psi}$	2.92 ± 0.20	T=0.713	T_q=0.321	T_L=0.436
	Time Mean	3.06 ± 0.17	2.85 ± 0.18	2.98 ± 0.19	3.07 ± 0.23	3.12 ± 0.18		$G X T$=0.239	$G X T_q$=0.089§	$G X T_q$=0.089§
SOD	P	0.49 ± 0.09	0.52 ± 0.11	0.50 ± 0.12	0.49 ± 0.08	0.49 ± 0.14	0.50 ± 0.02	G=0.198		G=0.285
(U/mL)	TC	0.45 ± 0.10	0.46 ± 0.16	0.47 ± 0.15	0.42 ± 0.15	0.48 ± 0.10	0.46 ± 0.02	T=0.687	T_L=0.756	T_L=0.155
	Time Mean	0.47 ± 0.02	0.49 ± 0.03	0.49 ± 0.03	0.46 ± 0.02	0.48 ± 0.03		$G X T$=0.808	$G X T_L$=0.564	$G X T_L$=0.656

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the response to reactive oxygen and nitrogen species production in addition to antioxidant activity at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.684). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. TBARS = Thiobarbituric acid reactive substances; TAS = Total antioxidant status; SOD = Superoxide dismutase; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

pre-run values throughout the recovery also approached significance. Delta post-hoc analyses demonstrated significant attenuation of serum IL-6 measures 60-min post-run from pre-run levels in TC compared to P (104% TC increase vs. 210% P increase). Serum IL-2 markers also showed significantly decreasing activity in TC compared to P and pre-run measures over the 48-h recovery (see Figure 11).

Anti-Inflammatory Response Markers

Table 20 presents the serum anti-inflammatory cytokine markers analyzed in response to exercise. The overall MANOVA analysis revealed a significant Wilks' Lambda effect over time ($p<0.001$), but no differences between groups over time ($p=0.88$). Univariate measures for all inflammatory markers demonstrated significant changes over time, peaking 60-min post-run. Accounting for running intensity utilizing an ANCOVA, serum IL-13 levels were significantly different across groups ($p=0.031$) and tended to be different between groups over time ($p=0.053$). Serum IL-13 markers decreased only 6% on average from pre-run over the 48-h recovery in P, compared to a 13% average decrease in TC. Specifically, at 60-min post-run, serum IL-13 markers increased 5% over pre-run values in P, but actually decreased 7% below pre-run in TC. The serum IL-13 group ($p=0.029$) and group by time ($p=0.014$) differences from pre-run levels over the recovery period were also significant (see Figure 11).

Clinical Markers of Immune-Related Complete Blood Counts

Table 21 demonstrates the immune response-related complete blood count markers analyzed in response to exercise. The overall MANOVA analysis demonstrated

Table 19: Pro-inflammatory Cytokines and Chemokines [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
TNF-α	P	2.34 ± 1.23	2.74 ± 1.22	3.02 ± 1.55	2.48 ± 1.04	2.49 ± 0.90	2.61 ± 0.26	G=0.922		G=0.654
(pg/mL)	TC	2.49 ± 0.98	2.82 ± 0.90	2.93 ± 1.36	2.60 ± 0.91	2.42 ± 0.82	2.65 ± 0.31	T=0.003*	T_q=0.003*	T_L=0.156
	Time Mean	2.40 ± 1.12	2.77 ± 1.08†	2.98 ± 1.45†	2.53 ± 0.97$^{\Psi\lozenge}$	2.46 ± 0.85$^{\Psi\lozenge}$		$G \times T$=0.779	$G \times T_L$=0.504	$G \times T_L$=0.151
IFN-γ	P	7.67 ± 6.52	8.02 ± 7.77	8.73 ± 9.49	7.36 ± 7.15	7.75 ± 7.78	7.91 ± 2.55	G=0.382		G=0.570
(pg/mL)	TC	10.96 ± 11.44	10.71 ± 9.14	11.51 ± 12.50	12.47 ± 17.61	11.68 ± 15.42	11.47 ± 3.08	T=0.604	T_q=0.184	T_L=0.424
	Time Mean	9.01 ± 8.81	9.12 ± 8.29	9.86 ± 10.67	9.44 ± 12.46	9.35 ± 11.41		$G \times T$=0.388	$G \times T_L$=0.456	$G \times T_q$=0.461
IL-1β	P	0.67 ± 0.15	0.85 ± 0.21	0.84 ± 0.19	0.75 ± 0.20	0.69 ± 0.16	0.76 ± 0.08	G=0.059§		G=0.058§
(pg/mL)	TC	0.93 ± 0.51	1.12 ± 0.58	1.05 ± 0.39	0.98 ± 0.44	0.93 ± 0.40	1.00 ± 0.09	T<0.001*	T_q<0.001*	T_L=0.559
	Time Mean	0.78 ± 0.36	0.96 ± 0.42†	0.92 ± 0.30†	0.85 ± 0.33$^{\Psi\lozenge}$	0.79 ± 0.30$^{\Psi\lozenge}$		$G \times T$=0.860	$G \times T_q$=0.662	$G \times T_L$=0.465
IL-2	P	1.18 ± 0.96	1.33 ± 1.10	1.51 ± 1.38	1.23 ± 0.85	1.27 ± 0.94	1.30 ± 0.28	G=0.939		G=0.786
(pg/mL)	TC	1.17 ± 1.20	1.64 ± 2.18	1.32 ± 0.99	1.12 ± 1.01	1.11 ± 1.06	1.27 ± 0.34	T=0.070§	T_q=0.001*	T_L=0.293
	Time Mean	1.17 ± 1.04	1.46 ± 1.60†	1.43 ± 1.22†	1.18 ± 0.90$^{\lozenge}$	1.21 ± 0.97$^{\lozenge}$		$G \times T$=0.290	$G \times T_L$=0.195	$G \times T_L$=0.089§
IL-6	P	0.63 ± 0.54^	0.75 ± 0.53^	2.33 ± 1.38$^{\dagger\Psi}$	0.69 ± 0.44^$^{\lozenge}$	0.68 ± 0.43	1.02 ± 0.19	G=0.017*		G=0.509
(pg/mL)	TC	0.94 ± 1.00	1.14 ± 1.27†	2.32 ± 1.69$^{\dagger\Psi}$	0.89 ± 0.97$^{\Psi\lozenge}$	0.79 ± 0.76$^{\Psi}$	1.21 ± 0.23	T<0.001*	T_q<0.001*	T_q=0.648
	Time Mean	0.76 ± 0.76	0.91 ± 0.90†	2.33 ± 1.48$^{\dagger\Psi}$	0.77 ± 0.69$^{\Psi\lozenge}$	0.72 ± 0.58$^{\Psi\lozenge}$		$G \times T$=0.550	$G \times T_L$=0.053§	$G \times T_L$=0.064§
IL-8	P	2.74 ± 1.58	2.84 ± 1.29	6.21 ± 3.51	2.94 ± 1.24	2.52 ± 1.01	3.45 ± 0.41	G=0.002*		G=0.637
(pg/mL)	TC	3.31 ± 1.87	3.24 ± 1.71	5.39 ± 2.78	3.26 ± 2.08	2.74 ± 1.47	3.59 ± 0.49	T<0.001*	T_q<0.001*	T_q=0.185
	Time Mean	2.98 ± 1.69	3.00 ± 1.46	5.88 ± 3.20†	3.07 ± 1.61$^{\lozenge}$	2.61 ± 1.20$^{\Psi\lozenge\#}$		$G \times T$=0.287	$G \times T_q$=0.269	$G \times T_q$=0.166
IL-12p70	P	1.79 ± 1.83	1.84 ± 1.75	1.95 ± 1.93	1.70 ± 1.56	1.81 ± 1.93	1.82 ± 0.42	G=0.009*		G=0.706
(pg/mL)	TC	1.54 ± 1.78	1.59 ± 1.52	1.75 ± 1.93	1.34 ± 1.29	1.27 ± 1.12	1.50 ± 0.51	T=0.012*	T_q=0.008*	T_q=0.893
	Time Mean	1.69 ± 1.78	1.74 ± 1.63	1.87 ± 1.89†	1.55 ± 1.44$^{\Psi\lozenge}$	1.59 ± 1.65$^{\Psi\lozenge}$		$G \times T$=0.310	$G \times T_q$=0.124	$G \times T_q$=0.167

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the pro-inflammatory response at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.302). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. TNF-α = Tumor necrosis factor alpha; IFN-γ = Interferon gamma; IL = interleukin; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

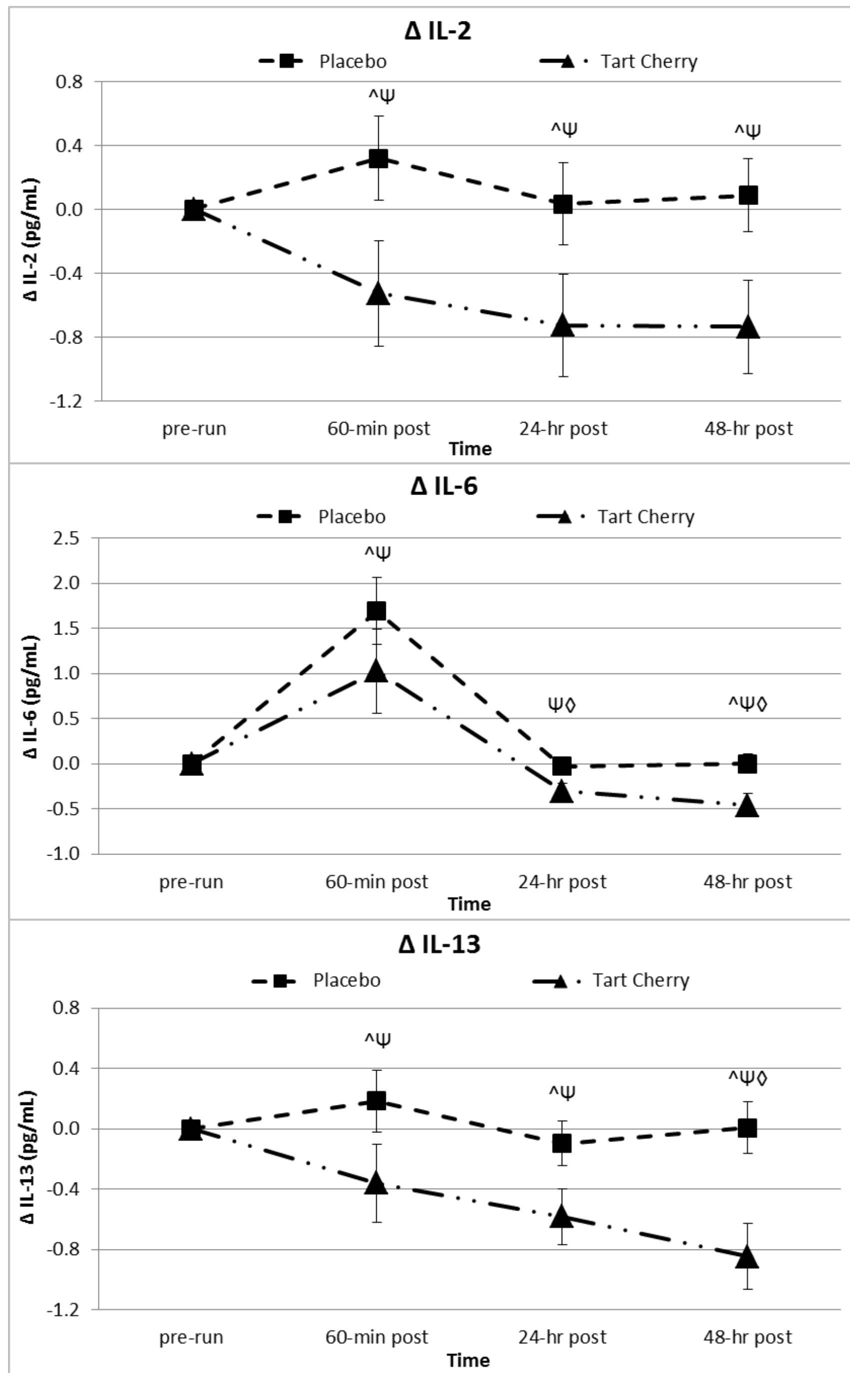

Figure 11. Markers of the Inflammatory and Anti-Inflammatory Response [Endurance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-run, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

significant Wilks' Lambda time interaction (p<0.001), but non-significant group changes over time (p=0.69). Univariate measures for all immune-related complete blood counts demonstrated significant changes over time. There were no significant changes in immune-related complete blood counts between groups over the study period.

Muscle Soreness Perception Assessment

Table 22 presents perceptions of muscle soreness across the resistance exercise protocol. Perceptions were not measured at baseline. The overall MANOVA analysis revealed a significant Wilks' Lambda time (p<0.001) interaction and group changes that tended to be different over time (p=0.093). Univariate measures for all locations of muscle soreness measurement demonstrated significant changes over time, peaking 60-min post-run. Significant differences between groups over time were found in vastus medalis (¼) soreness perception (p=0.035) that was confirmed when using an ANCOVA analysis to account for running intensity discrepancies. Subsequent post-hoc analysis indicated significantly attenuated pre-run vastus medalis (¼) soreness in TC compared to P with no differences in soreness perception between groups at any of the recovery time points (see Figure 12). The other two locations of quadriceps soreness perception testing did not reveal any significant differences between supplementation groups, particularly when accounting for running intensity using ANCOVA analyses. The change from pre-run vastus medalis (¼) soreness was smaller in P soreness perception compared to TC (p=0.035) over the 48-h recovery.

Table 20: Anti-inflammatory Cytokines [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
IL-4	P	4.57 ± 2.02	5.51 ± 2.31	5.20 ± 2.15	4.02 ± 1.49	4.21 ± 1.63	4.70 ± 1.28	*G*=0.304		*G*=0.165
(pg/mL)	TC	6.93 ± 8.98	8.71 ± 11.72	6.65 ± 6.37	5.41 ± 5.13	6.38 ± 7.03	6.82 ± 1.55	*T*=0.012*	T_q=0.012*	T_L=0.309
	Time Mean	5.53 ± 5.89	6.82 ± 7.64	5.79 ± 4.34	4.59 ± 3.45$^{\Psi\lozenge}$	5.09 ± 4.66$^{\Psi\lozenge\#}$		*G X T*=0.320	*G X* T_q=0.189	*G X* T_L=0.189
IL-5	P	0.57 ± 0.37	0.63 ± 0.42	0.66 ± 0.47	0.66 ± 0.46	0.61 ± 0.40	0.62 ± 0.14	*G*=0.102§		*G*=0.013*
(pg/mL)	TC	0.96 ± 0.75	1.01 ± 0.73	1.07 ± 0.76	1.01 ± 0.80	0.87 ± 0.59	0.98 ± 0.16	*T*=0.093§	T_q=0.013*	T_q=0.452
	Time Mean	0.73 ± 0.58	0.78 ± 0.59	0.82 ± 0.62	0.80 ± 0.63	0.71 ± 0.49$^{\Psi\lozenge\#}$		*G X T*=0.542	*G X* T_L=0.185	*G X* T_L=0.205
IL-7	P	3.75 ± 1.63	3.37 ± 1.57	4.66 ± 2.61	3.72 ± 1.81	3.47 ± 1.15	3.80 ± 0.43	*G*=0.295		*G*=0.427
(pg/mL)	TC	4.66 ± 2.54	4.27 ± 1.84	5.12 ± 2.22	4.55 ± 1.69	4.01 ± 1.42	4.52 ± 0.52	*T*<0.001*	T_q=0.010*	T_L=0.845
	Time Mean	4.12 ± 2.06	3.74 ± 1.71†	4.85 ± 2.42$^{\dagger\Psi}$	4.06 ± 1.78$^{\lozenge}$	3.69 ± 1.27$^{\lozenge\#}$		*G X T*=0.708	*G X* T_L=0.492	*G X* T_L=0.485
IL-10	P	2.91 ± 3.13	2.77 ± 1.89	24.17 ± 26.99	2.77 ± 1.78	2.68 ± 1.68	7.06 ± 1.36	*G*=0.683		*G*=0.948
(pg/mL)	TC	3.31 ± 2.74	3.99 ± 5.07	17.16 ± 18.60	3.66 ± 3.69	2.79 ± 1.98	6.18 ± 1.64	*T*=0.001*	T_q=0.001*	T_q=0.691
	Time Mean	3.07 ± 2.93	3.27 ± 3.51	21.31 ± 23.79$^{\dagger\Psi}$	3.13 ± 2.70$^{\lozenge}$	2.72 ± 1.77$^{\lozenge}$		*G X T*=0.421	*G X* T_q=0.495	*G X* T_L=0.509
IL-13	P	1.52 ± 0.95	1.77 ± 1.14	1.86 ± 1.27	1.55 ± 1.00	1.58 ± 0.86	1.65 ± 0.36	*G*=0.091§		*G*=0.031*
(pg/mL)	TC	2.56 ± 2.01	2.96 ± 2.37	2.74 ± 1.75	2.56 ± 2.00	2.40 ± 1.66	2.65 ± 0.43	*T*=0.006*	T_q=0.003*	T_q=0.027*
	Time Mean	1.94 ± 1.53	2.25 ± 1.80†	2.22 ± 1.52†	1.96 ± 1.54$^{\Psi\lozenge}$	1.91 ± 1.29$^{\Psi\lozenge}$		*G X T*=0.538	*G X* T_L=0.236	*G X* T_q=0.053§

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the anti-inflammatory response at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.447). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. IL = interleukin; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

Table 21: Markers of Immune-Related Complete Blood Counts [Endurance]

Variable	Group	Baseline	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
LYMPH (K/uL)	P	1.83 ± 0.58	2.50 ± 0.81	1.47 ± 0.54	2.04 ± 0.69	2.26 ± 0.35	2.02 ± 0.11	G=0.732		G=0.414
	TC	1.82 ± 0.53	2.63 ± 0.72	1.43 ± 0.25	1.75 ± 0.45	2.18 ± 0.46	1.96 ± 0.14	T<0.001*	T_q=0.013*	T_q=0.509
	Time Mean	1.83 ± 0.11	2.56 ± 0.15†	1.45 ± 0.09$^{\dagger\Psi}$	1.90 ± 0.12$^{\Psi\Diamond}$	2.22 ± 0.08$^{\dagger\Psi\Diamond\#}$		$G\ X\ T$=0.404	$G\ X\ T_L$=0.905	$G\ X\ T_L$=0.200
WBC (K/uL)	P	5.93 ± 1.45	6.54 ± 1.71	12.61 ± 3.39^$^{\dagger\Psi}$	6.64 ± 1.84$^{\Diamond}$	5.14 ± 0.84	7.37 ± 0.29	G=0.314		G=0.398
	TC	5.83 ± 1.50	6.85 ± 1.61	10.80 ± 3.40$^{\dagger\Psi}$	5.73 ± 1.20$^{\Diamond}$	5.33 ± 1.05	6.91 ± 0.35	T<0.001*	T_q<0.001*	T_L=0.613
	Time Mean	5.88 ± 0.29	6.70 ± 0.33†	11.71 ± 0.66$^{\dagger\Psi}$	6.18 ± 0.32$^{\Diamond}$	5.24 ± 0.18$^{\dagger\Psi\Diamond\#}$		$G\ X\ T$=0.223	$G\ X\ T_q$=0.162	$G\ X\ T_q$=0.500
MID (K/uL)	P	0.45 ± 0.14	0.53 ± 0.20	0.67 ± 0.23†	0.49 ± 0.19$^{\Diamond}$	1.10 ± 0.25$^{\dagger\Psi\Diamond\#}$	0.65 ± 0.03	G=0.477		G=0.607
	TC	0.43 ± 0.11	0.61 ± 0.19†	0.54 ± 0.15	0.40 ± 0.10$^{\Psi}$	1.10 ± 0.32$^{\dagger\Psi\Diamond\#}$	0.61 ± 0.04	T<0.001*	T_L=0.022*	T_q=0.495
	Time Mean	0.44 ± 0.03	0.57 ± 0.04†	0.60 ± 0.04†	0.44 ± 0.03$^{\Psi\Diamond}$	1.10 ± 0.06$^{\dagger\Psi\Diamond\#}$		$G\ X\ T$=0.276	$G\ X\ T_q$=0.388	$G\ X\ T_q$=0.562
GRAN (K/uL)	P	3.59 ± 1.07	3.53 ± 1.04	10.49 ± 3.49^$^{\dagger\Psi}$	4.09 ± 1.28$^{\Diamond}$	1.76 ± 0.59$^{\dagger\Psi\Diamond\#}$	4.69 ± 0.24	G=0.349		G=0.566
	TC	3.59 ± 1.41	3.64 ± 0.86	8.83 ± 3.35$^{\dagger\Psi}$	3.58 ± 0.98$^{\Diamond}$	2.05 ± 1.00$^{\Diamond}$	4.34 ± 0.29	T<0.001*	T_q<0.001*	T_L=0.326
	Time Mean	3.59 ± 0.24	3.58 ± 0.19	9.66 ± 0.67$^{\dagger\Psi}$	3.84 ± 0.23$^{\Diamond}$	1.90 ± 0.15$^{\dagger\Psi\Diamond\#}$		$G\ X\ T$=0.259	$G\ X\ T_q$=0.168	$G\ X\ T_q$=0.493
GM-CSF (pg/mL)	P	26.38 ± 41.92	25.49 ± 31.29	26.08 ± 34.72	22.64 ± 30.21	22.41 ± 29.72	24.60 ± 9.15	G=0.485		G=0.696
	TC	42.26 ± 47.28	37.37 ± 45.40	35.27 ± 46.54	29.52 ± 38.02	29.41 ± 36.03	34.77 ± 11.04	T=0.056§	T_L=0.022*	T_q=0.794
	Time Mean	34.32 ± 8.64	31.43 ± 7.36	30.68 ± 7.81	26.08 ± 6.57$^{\dagger\Psi\Diamond}$	25.91 ± 6.34$^{\dagger\Psi\Diamond}$		$G\ X\ T$=0.407	$G\ X\ T_L$=0.221	$G\ X\ T_L$=0.319

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the complete blood count immune response markers at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.684). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, † represents p<0.05 difference from baseline value, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. LYMPH = Lymphocytes; WBC = White blood cell; MID = Mid-range absolute count; GRAN = Granulocyte absolute count; GM-CSF = Granulocyte-macrophage colony-stimulating factor; RFT=race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

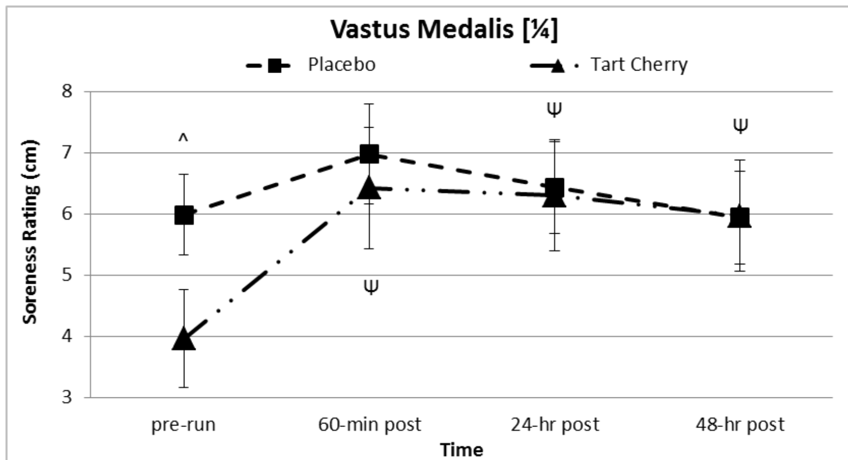

Figure 12. Perception of Quadriceps Muscle Soreness [Endurance]
Data expressed as means ± SE and LSD post hoc analysis is indicated by the following superscripts: ^ represents $p<0.05$ difference between groups, Ψ represents $p<0.05$ difference from pre-run, ◊ represents $p<0.05$ difference from 60-min post, # represents $p<0.05$ difference from 24-hr post.

Table 22: Quadriceps Muscle Soreness Perception [Endurance]

Variable	Group	Pre-Run	60-min Post	24-hr Post	48-hr Post	Group Mean	p-value (GG)	p-value (WSC)	RFT Covariate p-value (WSC)
Algo I (cm)	P	5.99 ± 2.94^	6.98 ± 3.35	6.44 ± 2.69	5.95 ± 3.01	6.34 ± 0.66	*G*=0.523		*G*=0.660
	TC	3.96 ± 2.15	6.43 ± 3.15$^{\Psi}$	6.31 ± 3.43$^{\Psi}$	5.98 ± 3.04$^{\Psi}$	5.67 ± 0.80	*T*=0.003*	T_q=0.002*	T_L=0.440
	Time Mean	4.98 ± 0.52	6.71 ± 0.64$^{\Psi}$	6.38 ± 0.59$^{\Psi}$	5.96 ± 0.59$^{\Psi}$		*G X T*=0.110	*G X* T_L=0.035*	*G X* T_L=0.028*
Algo II (cm)	P	5.02 ± 2.55	5.77 ± 2.91	5.58 ± 2.56	4.78 ± 3.02	5.29 ± 0.60	*G*=0.393		*G*=0.847
	TC	4.15 ± 2.66	5.12 ± 3.01	4.51 ± 3.10	4.08 ± 2.30	4.47 ± 0.72	*T*=0.122	T_q=0.013*	T_L=0.229
	Time Mean	4.59 ± 0.51	5.45 ± 0.58	5.05 ± 0.55	4.43 ± 0.54		*G X T*=0.921	*G X* T_q=0.889	*G X* T_q=0.458
Algo III (cm)	P	4.65 ± 3.04^	6.41 ± 2.91^$^{\Psi}$	6.04 ± 2.90^$^{\Psi\Diamond}$	4.41 ± 2.90$^{\Diamond\#}$	5.38 ± 0.67	*G*=0.098§		*G*=0.226
	TC	2.59 ± 2.45	4.43 ± 2.89$^{\Psi}$	3.48 ± 2.92	3.84 ± 3.11$^{\Psi}$	3.58 ± 0.80	*T*<0.001*	T_q<0.001*	T_L=0.508
	Time Mean	3.62 ± 0.55	5.42 ± 0.57$^{\Psi}$	4.76 ± 0.57$^{\Psi}$	4.12 ± 0.59$^{\Diamond}$		*G X T*=0.058§	*G X* T_q=0.053§	*G X* T_q=0.257

Individual group and time data expressed as means ± SD, while group effects are presented as means ± SEM. Data represents the participant soreness perception in the quadriceps muscle group at each test session during the 10 day intervention. MANOVA analysis revealed overall Wilks' Lambda time (p<0.001) and group x time (p=0.199). Univariate ANOVA p-levels from MANOVA analysis are presented for each variable. Univariate ANOVA p-levels are listed first by the Greenhouse-Geisser (GG) analysis and then by the within-subjects contrasts (WSC) to demonstrate the potential shape of the time or group x time interaction with significance indicated by the following super/subscripts: * indicates p<0.05 p-level significance, § indicates p<0.10 p-level significance. LSD post hoc analysis is indicated by the following superscripts: ^ represents p<0.05 difference between groups, Ψ represents p<0.05 difference from pre-lift, ◊ represents p<0.05 difference from 60-min post, # represents p<0.05 difference from 24-hr post. Algo I = Algometer location #1: Vastus Medalis 1/4; Algo II = Algometer location #2: Vastus Lateralis 1/4; Algo III = Algometer location #3: Vastus Lateralis 1/2; RFT = race finish time; G = group p-level; T = time p-level; G x T = interaction; q = quadratic p-level; L = linear p-level.

CHAPTER V

DISCUSSION AND CONCLUSION*

Tart Cherry Resistance

Introduction

This is the first study to investigate the effect of freeze dried Montmorency tart cherry skin powder on acute resistance exercise performance and recovery. It was hypothesized that supplementation with this novel powdered tart cherry skin supplement surrounding an acute bout of intense resistance exercise would reduce perceptions of muscle soreness, markers of muscle damage, oxidative stress, and inflammation, thus better maintaining subsequent performance within the first 48-h of recovery. The results of the present study demonstrate that this powered tart cherry formulation is effective in promoting decreased perceptions of muscle soreness following intense resistance exercise. Tart cherry powder reduced perceptions of muscle soreness in the distal vastus medalis and lateralis. In accordance with decreased perceptions of muscle soreness, tart cherry powder supplementation reduced serum markers of muscle catabolism and physiological stress over the 48-h post-lift period compared to placebo. As a result of the resistance exercise, markers of oxidative stress, lipid peroxidation, and antioxidant activity did not significantly change over time and was not affected by differences in supplementation. The inflammatory response increased from pre-lift values during the

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*Portions reprinted from “Effects of powdered Montmorency tart cherry supplementation on an acute bout of intense lower body strength exercise in resistance trained males” by Levers K, Dalton R, Galvan, E, et al. 2015. *Journal of the International Society of Sport Nutrition*, 12, 1-23, Copyright 2015 by Kyle Levers.

recovery period, but the change was not significantly different between supplement groups.

The attenuation of quadriceps muscle soreness in conjunction with reduced hemodynamic markers of muscle catabolism following the resistance training bout indicates that the consumption of tart cherry powder dampened the effects of the secondary muscle damage response. The initial injury to the muscle microstructure is defined by a mechanical disruption of the myofibrils, particularly in response to high volume and intensity eccentric exercise (35, 53, 76). The damage to the muscle microstructure triggers a local inflammatory response characterized by infiltration of fluid, plasma proteins, and free radicals that all exacerbate the initial mechanical muscle damage, creating a secondary injury incidence (4, 31, 35, 76, 111, 171). Decreased perceptions of quadriceps muscle soreness and muscle catabolism indices reveal that supplementation with powdered tart cherry aids in blunting the secondary muscle damage effects compared to placebo.

Muscle Soreness Perception

The apparent beneficial effect of tart cherry powder supplementation on the perception of muscle soreness after a resistance exercise bout is consistent with some of the previously published findings. Connolly et al. (40) reported that consumption of a Montmorency tart cherry juice in healthy college-aged males significantly reduced pain in the elbow flexors after a bout of eccentric exercise using a visual analog scale (VAS). Peak muscle pain was achieved 24-h post-exercise in the tart cherry group compared to a

continued increase in pain 48-h post-exercise in the placebo group. In contrast, Connolly et al. (40) reported no difference in pressure pain threshold (PPT) scores between the two experimental groups. Using a strenuous single leg knee extension protocol in a cohort of well-trained male athletes, Bowtell et al. (20) demonstrated a trend in post-exercise muscle pain reduction via PPT with Montmorency tart cherry juice supplementation up to 48-h post-exercise compared to placebo. The positive results in the current study are similar to previous tart cherry supplementation research findings, showing that powdered tart cherry supplementation significantly attenuates muscle soreness perceptions throughout the 48-h post-lift recovery compared to placebo. Slight differences in study outcomes may lie in the disparity of muscle pain or soreness measures, tart cherry supplements, quantity of musculature involvement, and/or exercise modality. With respect to the disparity among the discussed research, Connolly et al. (40) utilized both a VAS and a separate PPT in upper extremity exercise, Bowtell et al. (20) only utilized PPT surrounding single leg exercise, while the current study employed a combination of constant pressure with a GPRS (version of VAS). Measurement of muscle soreness perception in the present study utilizing both an algometer and a GRPS was implemented to help ameliorate the purely subjective nature of a VAS as the only measure of pain or soreness.

Muscle Damage and Catabolism

The attenuation in post-lift muscle soreness with powdered tart cherry supplementation may be described by underlying catabolic mechanisms. Similar to the

results of the current study, Bowtell et al. (20), following exhaustive leg extension exercise, demonstrated a faster post-exercise recovery of knee extensor force coupled with a trend for a smaller CK percent change from pre-exercise levels up to 48-h post-exercise with tart cherry supplementation compared to placebo (9). Following a treadmill incremental exercise protocol with thoroughbred horses, Ducharme et al. (50) reported an attenuation trending toward significance in CK levels during exercise recovery when supplementing with a tart cherry juice blend compared to placebo. Similar to the post-lift attenuations of ALT (60-min and 48-h post) and AST (48-h post) as secondary markers of muscle damage in the current study, Ducharme et al. (50) reported that AST was significantly mitigated during and following an incremental exercise protocol in the tart cherry-treated horses compared to placebo (9). In an endurance-based crossover study examining the effects of acute ibuprofen (8400 mg) ingestion surrounding a 45-min downhill treadmill run, Donnelly et al. (48) reported an increase in serum CK, AST, and lactate dehydrogenase post-run with maximal activity of CK and AST occurring at 24-h post-run, while lactate dehydrogenase, creatinine, and urea peaked 6-h post-run. Donnelly et al. (48) revealed that serum CK and urea levels were significantly higher after ibuprofen supplementation compared to placebo throughout the post-run recovery. Analyzing hemodynamic clinical chemistry makers before, 4-h, and 24-h post-Boston marathon, Kratz et al. (99) reported significant increases in total CK, AST, ALT, total protein, uric acid, and creatinine 4-h post-race and confirmed that CK, creatinine, uric acid, ALT, and AST remained significantly

elevated over pre-race values 24-h post-race. The attenuation of these markers in the current study, demonstrates beneficial powdered tart cherry supplementation effects on the post-resistance exercise catabolic, muscle damage, and stress response.

Inflammatory Response

Acute, intensive resistance exercise (> 60% 1-RM) has been reported to significantly increase muscular mechanical trauma as the initial phase of injury (20, 78) coupled with a secondary inflammatory injury phase that occurs as a result of plasma protein and inflammatory cell infiltration of the damaged tissue (20, 35, 111). In a strength-based supplement study with resistance trained subjects, Bowtell et al. (20) was also not able to detect any significant effects on IL-6 as a marker of inflammation. Further, Trombold et al. (189) reported similar non-significant inflammatory (IL-6) findings in a study involving non-resistance trained subjects performing repeated bouts of eccentric elbow flexor muscle contractions with consumption of pomegranate-derived ellagitannin (20). Supplementation in the current study did not affect the inflammatory response to muscular trauma as markers peaked 60-min post-lift with no response differences between supplementation groups. Attenuation of muscle soreness perceptions and markers of muscle damage are not likely attributed to changes in inflammation following a single resistance exercise bout. Differences in results between studies are likely attributed to variation in intensity, duration, and modality of the aforementioned exercise protocols.

Catabolic and Physiological Stress Hormone Response

The increase in inflammatory-related cytokines and chemokines such as TNF-α, IL-1β, IL-6, and IL-8 during and immediately following exercise has been shown in previous research (63, 134, 138) and closely resembles the inflammatory response in the current study. As described in previous literature, the increase in serum IL-6 within both groups 60-min post-lift in the current study can likely be attributed to the large release of muscle-derived IL-6 as a result of the contracting muscle fibers (63, 175). The influx of muscle-derived IL-6 within the systemic circulation may be one of the triggers for subsequent cortisol release in response to exercise-induced stress (63, 174). Glucocorticoids, specifically cortisol, and anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 are released during strenuous exercise and typically demonstrate an immunosuppressive influence to help modulate the immune response balance (64). However, extended immunodepression due to elevated plasma cortisol during the post-exercise period, particularly following long bouts of intense training in the fasted state (63), may hinder recovery and subsequent performance. Previous research conducted by McAnulty et al. (116) in trained endurance athletes reported a significant cortisol increase over time, but no significant difference in immediate and 1.5-h post-race cortisol levels with 2-month vitamin E supplementation compared to placebo. Comparing 14-d supplementation of *N*-acetyl-cysteine (NAC), epigallocatechin gallate (EGCG), or a placebo in active males surrounding a single bout of eccentric knee-extensor exercise, Kerksick et al. (94) found a significant decrease in serum cortisol

levels 6-h post-exercise, but no differences between groups up to 72-h post-exercise despite a significant blunting of muscle soreness perception 24-h post exercise in the two supplement groups compared to placebo. The current study demonstrated an increase in cortisol levels 60-min post-lift compared to pre-lift in both groups. However, unlike the cortisol and muscle soreness perception results reported by Kerksick et al. (94), the current study demonstrated significantly elevated cortisol levels and muscle soreness in the placebo group compared to the powdered tart cherry group 24-h and 48-h post-lift.

Immune Cellular Counts

The placebo group elevations in serum cortisol levels in the latter recovery period may be linked to differences in the immune response and the degree of secondary muscle injury. Previous research by McCarthy et al. (118) and Robson et al. (158) demonstrate that in response to repetitive muscular contraction during and immediately after acute, intense exercise, there is a large increase in circulating neutrophils (GRAN) and lymphocytes. According to data collected by Robson et al. (158), plasma neutrophil levels tend to peak 2-3 hours post-exercise, but remain elevated above pre-exercise levels for up to 10-h post-exercise due to elevations in plasma cortisol (e.g. perception of stress) that facilitate the release of neutrophils from the bone marrow. The current study demonstrated a plasma neutrophil (GRAN) peak 60-min post-lift, but effects of supplementation could not be determined as levels returned to pre-lift concentrations by 24-h. Unlike the neutrophil response to acute exercise, lymphocytes respond in a biphasic pattern, where plasma levels are significantly elevated during and immediately

post-exercise followed by a drop below pre-exercise levels during the initial recovery period due to a efflux from the blood circulation, and a slow return to baseline levels as equilibrium is reached again (64, 158). Robson et al. (158) demonstrated that serum cortisol levels influence both the influx of neutrophils and efflux of lymphocytes from systemic circulation. The results of the current study demonstrated that lymphocyte levels in the placebo group never returned to pre-lift levels during the 48-h recovery. This may be linked to the elevated plasma cortisol levels in the placebo group representing an increased physiological perception of exercise stress 48-h post-lift compared to pre-lift and powdered tart cherry group levels. As previously mentioned, the secondary injury phase occurs as a result of significant plasma protein and inflammatory cell influx within the damaged tissue (20, 35, 111). Powdered tart cherry supplementation may have aided in reducing secondary muscular injury through an initial dampening of the immune response paired with the attenuated cortisol response later in exercise recovery. However, immune cell count changes in response to supplementation and the resistance exercise stimulus are speculative due to the lack of cellular count data corresponding to typical patterns of immune cell responses during and immediately following the barbell back squat challenge.

Free Radical Production, Antioxidant Response, and Redox Balance

The increase in antioxidant bioavailability from tart cherries containing high levels of flavonoids and anthocyanins (166, 199) has been hypothesized to be one of the main benefits of tart cherry supplementation. Antioxidant bioavailability is important in

maintaining adequate redox balance to support the endogenous antioxidant systems following excessive ROS-producing strenuous exercise. Ducharme et al. (50) investigated the effects of Montmorency tart cherry juice supplementation on oxidative stress in thoroughbred horses following a stepwise incremental treadmill running protocol (9). Overall indications of oxidative stress as a result of exercise were reported through significant elevations in lipid hydroperoxidation (TBARS) (50), but similar to the current study, no differences between groups were shown. In an endurance study examining the effects of tart cherry juice supplementation on oxidative stress following a marathon run, Howatson et al. (76) demonstrated significantly lower TBARS levels in the tart cherry supplemented group versus placebo 48-h post-marathon. As a highly reactive oxide metabolite of nitric oxide, peroxynitrate-bound tyrosine residues forming nitrotyrosine (NT) (196) were measured by Sureda et al. (178) following supplementation of vitamin C + E surrounding a half-marathon. Suerda et al. (178) reported a significant increase in both NT immediately post-race and 3-h post-race in the placebo group compared to the vitamin C + E supplemented group, indicating that antioxidant supplementation may have an attenuating effect on the oxidation of nitrogen-containing compounds surrounding endurance exercise. Contrarily, both Bowtell et al. (20) and the current study found no difference between supplementation groups with regard to oxidation of nitric oxide (NT) in the post-strength exercise period. A difference in outcome may be attributable to the difference in exercise modality and thus the minimal reliance on aerobic metabolism demands during resistance exercise.

Further, evidence in the literature utilizing lipid peroxidation (TBARS) analyses have presented a potential lack of oxidative damage detection specificity in human studies that may also explain the variability in results between the current and previous studies (9, 12, 13, 193).

In a study analyzing the recovery from a marathon run, Howatson et al. (76) analyzed plasma TAS, as a measure of antioxidant or antiradical activity (84), and found that TAS fell below baseline 48-h post-marathon in the placebo group (9). Unlike the tart cherry group, the placebo group failed to maintain TAS or redox balance following the endurance exercise, demonstrating possible antioxidant effectiveness on excessive ROS production with bouts of endurance exercise (9). Childs et al. (32) analyzing TAS following arm eccentric exercise-induced injury demonstrated significantly greater TAS levels with vitamin C + NAC supplementation compared to placebo 48-h through 7-d post-exercise in healthy, untrained males. A resistance training-related study conducted by Lafay et al. (102) investigating the effects of a polyphenol-rich grape extract on repeated jumping force capacity, found a significant jumping force capacity improvement in the grape extract group over placebo. However, similar to the current study, Lafay et al. (102) found no significant difference in SOD activity between the groups. The current resistance training study also did not demonstrate any significant change in TAS activity across time or between groups possibly attributed to differences in study population and the low metabolic cost associated with resistance/eccentric exercise versus endurance exercise.

Research Investigation Strengths and Weaknesses

The strengths of this particular study revolve around the analysis of a large cohort of muscle soreness, performance, muscle damage, inflammatory, and oxidative damage measures to contribute a comprehensive analysis to the existing body of published literature. This type of comprehensive hemodynamic analysis has not been conducted in a tart cherry supplement study paired with resistance exercise. Further, the current study employed one of the largest subject cohorts among recent studies examining polyphenolic, vitamin, or NSAID supplementation effects on performance and related hemodynamic markers. The utilization of this supplement within the free-living resistance trained population demonstrated its effectiveness under normative training, diet, and performance conditions. The ease associated with consuming an encapsulated powdered supplement versus a potentially inconvenient or unpalatable juice most likely enhanced subject compliance with supplementation. Potential limitations and weakness of the current study should also be considered. The placebo-control matched design of this study was effective in equalizing study subject exposure to the resistance protocol irrespective of supplement group, however compared to a cross-over design, there might have been some variability associated with subject pairing. Differences in resistance training experience and overall state of training beyond the study inclusion/exclusion criteria may also have been a source of variability in study cohort recruitment. Due to the large number of hemodynamic markers measured in this study, the five selected time points of blood draws over the course of

the experimental period may have not captured the entire pharmacokinetic profile for each marker. Despite controlling 48-h training activity and acute NSAID intake with a 10-h fast before each session, nutritional intake and hydration status of each subject was not controlled nor tested. Differences in nutrition and hydration among study subjects could have been a potential source of variability in hemodynamic markers or performance measures in a cohort of this size. The 48-hour NSAID ingestion limitation may not have been a sufficient washout time for all NSAID-type medications considering the large range in reported half-life of common NSAIDs (1.6 to 30-h), which may have also been a contributing source of acute variability. However, chronic or habitual NSAID users were excluded from the study pool during the initial study screening process, so the 48-h NSAID restriction was utilized as a secondary control point to help eliminate potential effects of acute NSAID ingestion and strengthen study validity. The major overriding strengths of this study are that this is the first practical study to be conducted surrounding an acute bout of strength exercise incorporating significant muscle mass recruitment and it is the first study to be conducted utilizing a powdered form of cherries rather than a juice or concentrate.

Conclusion

The current study demonstrated that consumption of a Montmorency powdered tart cherry supplement 7-d before, the day of, and 2-d after completing a single bout of high volume, high-intensity resistance exercise, appears to be an effective dietary supplement in reducing muscle soreness in the most biomechanically loaded region of

the quadriceps near the distal patellar attachment and markers of muscle catabolism in resistance trained individuals. Short-term supplementation with powdered tart cherry surrounding a single bout of resistance training did not demonstrate any definitive effect on markers of oxidative damage or inflammation. Due to the inconclusive oxidative damage and inflammatory evidence, mechanisms of short-term powdered tart cherry and other related phytochemical-containing nutritional supplements surrounding bouts of high intensity, anaerobic and resistance exercise need to be further investigated. Additional examination of powdered tart cherry supplementation with other forms of exercise that are known to promote a more pronounced effect on inflammation and oxidative stress (e.g. endurance exercise) is also needed. However, the initial effectiveness in reducing perceptions of muscle soreness and markers of muscle catabolism in resistance-trained men demonstrates that powdered tart cherry supplementation provides similar benefits as previously studied tart cherry juices or concentrates following acute bouts of lower body strength-based exercise.

Tart Cherry Endurance

Introduction

Previous research has investigated the efficacy of tart cherry supplementation surrounding bouts of endurance exercise, however, this is the first study to investigate the effect of Montmorency tart cherry skin powder on acute endurance performance recovery. It was hypothesized that supplementation with this novel powdered tart cherry skin supplement prior to a single bout of high volume endurance exercise would

attenuate markers of muscle damage, oxidative stress, inflammation, and perceptions of muscle soreness in facilitation of faster recovery. Tart cherry ingestion reduced post-run serum markers of muscle catabolism, secondary muscle damage, and physiological stress over the 48-h recovery period compared to the placebo. Reduced serum markers of muscle catabolism and stress are indicative of the attenuated 48-h recovery inflammatory response with tart cherry supplementation versus placebo. Despite lower levels of TAS activity observed in the tart cherry group prior to performing the run versus those supplemented with the placebo, antioxidant activity in those who ingested tart cherry was greater than the placebo, particularly 24-h and 48-h post-run. Despite increases in actual race pacing over projected race pace times reported from previous running performances in both groups, the tart cherry group demonstrated smaller pace differences compared to placebo. Medial quadriceps soreness in tart cherry supplementers was significantly lower pre-run compared to those ingesting the placebo. However, results indicated a smaller change from pre-run medial quadriceps soreness in placebo supplementers over the 48-h recovery period compared to the tart cherry group.

Endurance Performance

Despite significantly faster half-marathon finish race times and a smaller difference between projected and actual race pace reported in the tart cherry group compared to the placebo group in the current study, the performance benefits cannot solely be attributed to differences in supplementation due to the study design not including a monitored pre-supplementation half-marathon run as a basis for comparison.

Compared to projected race pacing, the increase in actual race pace is likely attributed to the 10-h fast and blood draw prior to the day of the endurance exercise challenge that would have not been experienced prior to any other race. The apparent beneficial effect of tart cherry powder supplementation on the increase in endurance performance through a decrease in race completion time is consistent with some of the previously published findings in the exercise and polyphenol supplementation literature. In a study conducted on aerobically fit males and females, Davis et al., supplemented 500 mg/d of quercetin or placebo for 7-d prior to an incremental VO_2 max test on a cycle ergometer and a cycling time trial to fatigue on the same ergometer (44). Davis et al. demonstrated an increase in both VO_2 max and ride time to fatigue following quercetin supplementation compared to placebo (44). Nieman et al. conducted a study in young, healthy males with 2-wk of quercetin supplementation (1000 mg/d) versus placebo (132). Following a 12-min treadmill running trial at a 15% grade and self-selected speed, Nieman et al. reported a significantly greater pre-supplementation versus post-supplementation change in distance covered with quercetin supplementation versus placebo (132). The polyphenol content of fruit-derived supplements similar to tart cherry were proven beneficial after 30-d of supplementation in a study conducted by Kang et al. on regular endurance exercisers (89). Kang et al. demonstrated that 30-d supplementation of oligomerized lychee fruit extract significantly elevated both submaximal running time and anaerobic threshold compared to a vitamin C/E mixture and a placebo (89). The difference in race pace and times within the current study may have correlated to a

discrepancy in running intensity between the groups, thus utilization of half-marathon finish time as a covariate in a separate ANCOVA statistical analysis was necessary to determine if significant statistical interactions were attributed to differences in running intensity or supplementation.

Muscle Damage and Catabolism

Attenuation of muscle catabolism and secondary markers of muscle damage following prolonged endurance exercise physiologically provides the body optimal conditions for quicker recovery and repair in preparation for subsequent performance bouts. Studying trained endurance runners, Kratz et al. (99) analyzed hemodynamic clinical chemistry makers before, 4-h, and 24-h post-Boston marathon. The results of demonstrated significant increases in total CK, AST, ALT, total protein, uric acid, total bilirubin, BUN, and creatinine 4-h post-race and confirmed elevations in CK, BUN, creatinine, uric acid, ALT, and AST remaining significantly greater than pre-race values 24-h post-race (99). This study demonstrates normative changes in markers of muscle catabolism following acute bouts of high volume endurance exercise in trained endurance athletes. In an eccentrically-braked endurance running study, Donnelly et al. (48) acutely supplemented subjects with ibuprofen (8400 mg) surrounding a 45-min downhill treadmill run. Donnelly et al. (48) documented a post-run increase in serum CK and AST with maximal activity occurring at 24-h of recovery, while both serum creatinine and urea markers peaked 6-h post-run. Bell et al. (13) in an acute endurance study following a combination of cycling sprints and time trials reported results similar

to the current study, demonstrated no differences in the CK response between Montmorency tart cherry concentrate and placebo supplementation. Unlike the current acute endurance study, Howatson et al. (76) following marathon running demonstrated a trend of lower post-resistance exercise CK levels when supplementing with tart cherry juice compared to placebo up to 48-h of recovery. Despite conflicting evidence among previous endurance-supplemented tart cherry research, the post-run attenuation of these markers in the current study within the powdered tart cherry group, demonstrates a beneficial effect of supplementation on indices of muscle catabolism.

Inflammatory Response

Previous research in the literature seems to conclude that the inflammatory process is mediated by both pro-inflammatory cytokines (63) and neuroendocrinological factors (138). However, it has also been demonstrated that as major players in the development of secondary muscle damage, neutrophils, may also amplify the release of inflammatory cytokines (26, 172). Nieman et al. (131) supplemented trained cyclists with quercetin, quercetin-EGCG (epigallocatechin 3-gallate), or placebo soft chews for 24-d surrounding 3-d of consecutive bouts of 3-h submaximal cycling. Nieman et al. (131) reported a significant decreases in plasma concentrations IL-6 immediately post-exercise on the third exercise day in the quercetin-EGCG group compared to placebo (131). Howatson et al. (76) reported significantly lower inflammation through analysis of IL-6 after running a marathon that coincided with quicker recovery of knee extensor maximal strength following the marathon in Montmorency tart cherry juice

supplemented subjects compared to placebo. IL-6 markers where significantly attenuated immediately post-race with tart cherry consumption compared to placebo (9, 76). Coinciding with reduced inflammatory findings of Nieman et al. (131) and Howatson et al. (76) following endurance challenges, the current half-marathon study also reported a post-run attenuation in IL-6 with powdered tart cherry supplementation versus placebo. Similar to the reduction in anti-inflammatory response (IL-10) in the quercetin-EGCG group immediately following a submaximal cycling bout published by Nieman et al. (131), the powdered tart cherry group in the current study also demonstrated similar changes via an attenuated IL-13 response over the 48-h recovery compared to placebo.

Catabolic and Physiological Stress Hormone Response

Glucocorticoids, specifically cortisol, released due to activation of the stress response through muscle mechanical microtrauma and ROS production have demonstrated an immunosuppressive influence. Davison and Gleeson (45), in an investigation of moderately trained males during 2.5-h moderate intensity cycling compared the effects of a beverage containing a vitamin C supplement with and without carbohydrate before and during endurance exercise. The study by Davison and Gleeson (45) revealed a significant increase in plasma cortisol levels immediately and 1-h post-exercise in both the placebo and vitamin C only supplemented groups with no significant difference between these two groups at 1-h post-exercise (45). The addition of carbohydrates (alone or with vitamin C) significantly lowered the cortisol response

during the exercise recovery up to 1-h post-exercise (45). This result demonstrates a potentially lower physiological stress in the short-term post-exercise period due to a higher energy state. The results of the current study revealed a similar cortisol response 60-min and 24-h post-run as both fasted groups demonstrated an increase from pre-run values, but the placebo group response from pre-run values was significantly greater than tart cherry group levels. Based on the findings reported by Davison and Gleeson (45), the attenuation of the cortisol response 60-min post-run may be due to a combination of anti-inflammatory and antioxidant effects of tart cherry anthocyanins.

Due to the reduced cortisol response 60-min post-run following tart cherry supplementation in the current study, it is likely that this anthocyanin-rich supplementation may modulate endogenous cytokine secretion following stressful exercise challenges. This tart cherry anthocyanin modulation resulted in an attenuated release of IL-6 throughout the 48-h post-run recovery compared to placebo. An acute supplementation study providing moderately active subjects with 48 g of anthocyanin-rich black currant extract immediately surrounding a single bout of high-intensity rowing conducted by Lyall et al. (109) demonstrated a significant post-exercise attenuation of pro-inflammatory cytokine production from LPS-stimulated cells. Lyall et al. (109) postulated from subsequent in vitro experimentation that this reduced cytokine production may have resulted from anthocyanin-based inhibition of NF-κB-mediated mechanisms. In the current study, attenutated IL-6 levels over the 48-h recovery with tart cherry supplementation coupled with lower recovery serum cortisol levels compared

to the placebo group, demonstrates a potential relationship between the perception of physiological stress, regulation of anti-inflammatory cytokines, and cortisol release through NF-κB-mediation.

Free Radical Production, Antioxidant Response, and Redox Balance

The attenuation muscle catabolic indices demonstrated in the current study may also be partially attributed to an improved post-run redox balance with tart cherry supplementation compared to placebo. The increase in antioxidant bioavailability from acute tart cherry supplementation containing high levels of flavonoids and anthocyanins (166, 199) has been hypothesized to be one of the primary benefits in support of endogenous antioxidant systems following strenuous exercise and excessive ROS-production. Howatson et al. (84) analyzed plasma TAS, as a measure of antioxidant or antiradical activity across all biological components, following a full marathon in trained endurance runners, and found that TAS was significantly greater in the tart cherry supplemented group compared to control across all time points (pre-race and up to 48-h post-race) (9, 76, 172). Unlike the tart cherry group, TAS levels dropped below baseline 48-h following endurance exercise in the placebo group as they failed to maintain redox balance. This discrepancy between supplementation groups demonstrates possible tart cherry antioxidant effectiveness on excessive ROS production with bouts of endurance exercise (9). The current study reported lower pre-run TAS levels in the tart cherry group compared to placebo. However, similar to the recovery findings of Howatson et al. (84), the current study revealed a linear increase in TAS activity culminating in a 48-

h recovery TAS activity that was greater in the tart cherry group compared to placebo. Despite a different exercise protocol and antioxidant supplement, Childs et al. (32), analyzing TAS following arm eccentric exercise-induced injury also demonstrated significantly greater TAS levels with vitamin C + NAC supplementation compared to placebo 48-h through 7-d post-exercise recovery in healthy, untrained males. Interestingly, in a study conducted in trained cyclists by Morillas-Ruiz et al. (125), subjects performed a 90-min submaximal endurance time trial on a cycle ergometer while consuming a commercial antioxidant beverage containing fruit concentrates and carbohydrates over the course of the entire testing protocol. Morillas-Ruiz et al. (125) found no difference in TAS immediately and 45-min post-exercise between antioxidant beverage and placebo groups. Contradictory results may have been attributed to the limited supplementation and recovery analysis time table as well as the supplement itself. This demonstrates a potentially short-term antioxidant effect of powdered tart cherry consumption surrounding a single endurance challenge with better achievement of redox balance compared to placebo supplementation.

The reduction in the hemodynamic markers of muscle catabolism and enhanced redox balance in the current study demonstrate beneficial effects of supplementation. Ducharme et al. (9) piloted the first endurance-based study to investigate the effects of Montmorency tart cherry juice supplementation on oxidative stress created by an exhaustive incremental treadmill running protocol in thoroughbred horses. Overall indications of exercise-induced oxidative stress were reported through significant

elevations in lipid hydroperoxidation decomposition products over time as measured by TBARS (58), but similar to the current study, no differences between groups were reported (50). In an endurance study, similar to the current protocol, Howatson et al. examined the effects of tart cherry juice supplementation on oxidative stress following a marathon run. Supplementing with a tart cherry juice blend or placebo for 8-d surrounding the marathon, Howatson et al. (76) demonstrated significantly lower TBARS levels 48-h post-marathon in the tart cherry supplemented group versus placebo. In coordination with Howatson et al. (76), Pilaczynska-Szczesniak et al. (144) reported significantly attenuated serum TBARS levels at 1-min and 24-h post-2,000 m incremental rowing test following 4-wk of chokeberry supplementation in trained rowing athletes compared to those supplemented with the placebo. In two more recent studies within the same trained rowing athlete population used by Pilaczynska-Szczesniak et al. (144), Skarpanska-Stejnborn et al. (168, 169) reported no differences in post-2,000 m incremental rowing test TBARS levels following 4-5-wk of supplementation with either *Rhodiola rosea L.* extract or artichoke extract. Contradictory outcomes between studies may be due to mode of exercise, training and nutrition status, and duration of supplementation. Further, evidence in the literature utilizing lipid peroxidation (TBARS assays) analysis has presented a potential lack of oxidative damage detection specificity in human studies that may also explain the variability in results between the current and previous studies (9, 12, 13, 193).

As a highly reactive oxide metabolite of nitric oxide, peroxynitrate-bound tyrosine residues forming nitrotyrosine (NT) (196) was measured by Sureda et al. (178) following supplementation of vitamin C + vitamin E surrounding a half-marathon. Suerda et al. (178) reported a significant increase in NT immediately post-race and 3-h post-race in the placebo group compared to the vitamin C + vitamin E supplemented group, indicating that antioxidant supplementation may have a dampening effect on oxidation of nitrogen-containing compounds with endurance exercise. Contrarily, a previous tart cherry study conducted by Bowtell et al. (20) surrounding an intensive resistance exercise workout of repeated leg extensions in resistance trained males found no difference in serum nitrotyrosine measures between supplementation groups in the post-strength exercise period. The current study also reported no differences in NT levels over the study protocol and between supplementation groups. The outcome inconsistency may also be attributable to the differences in exercise modality or antioxidant supplement, thus exhibiting a disparity in metabolic system reliance for energy production and potential mechanistic variability in whole fruit-derived versus extracted antioxidant supplements (e.g. vitamins C and E).

Muscle Soreness Perception

The effect of phytochemical or vitamin containing anti-inflammatory supplements on the perception of muscle soreness after an endurance exercise challenge is inconsistent within the literature. In an endurance relay race-based study with trained runners (average running distance 26.3 km), Kuehl et al. (101) used a VAS to track

muscle pain and found that those who supplemented with a Montmorency tart cherry juice blend had significantly lower post-race pain compared to a placebo. Due to the nature of this endurance event, the post-race pain measurement timeline and individual running segment distances were not standardized across all participants (9, 101). Similarly, in an eccentrically breaking endurance trial where physically active subjects ran downhill continuously for 30-min and were acutely supplemented with either ascorbic acid or a placebo, Close et al. (37) reported no significant differences in VAS pain ratings nor pressure algometry between groups up to 14-d post-exercise on six lower extremity locomotion muscle groups. With no effect on post-aerobic exercise delayed onset muscle soreness (DOMS) coupled with previous evidence in the literature, Close et al. (37) suggested a dissociation between post-exercise ROS production and DOMS. Following a marathon running event and a bout of high intensity stochastic cycling using a similar 200 mm VAS protocol, Howatson et al. (76) and Bell et al. (13) respectively, reported no difference in DOMS ratings between Montmorency tart cherry juice supplementation and placebo up to 72-h post-exercise. Within the current study, the pre-run perception of vastus medialis muscle soreness was significantly greater in the placebo group compared to tart cherry with no soreness differences between groups over the three recovery time points. Due to the significant difference in pre-run medial quadriceps soreness between supplementation groups, delta changes calculated from pre-run revealed greater recovery muscle soreness with tart cherry supplementation compared to placebo. Without a baseline measure of quadriceps soreness perception and

a subject training load record before the start of the study or beyond the 48-h pre-testing session exercise limitation, it is difficult to rationalize the pre-run muscle soreness discrepancy. However, the variability in soreness perceptions across muscle groups within the current study compared to previous research may also be due to the disparity in measurement protocol, tart cherry supplements, exercise modality, and/or subject pool training status. Limited muscle damage in the current study may also be attributed to the minimal changes in elevation over the duration of the flat race course, which minimized excessive eccentric loading during the run. Measurement of muscle soreness perception in the present study utilizing both an algometer and a GRPS was implemented to help ameliorate the purely subjective nature of a VAS as the only measure of pain or soreness.

Research Investigation Strengths and Weaknesses

The strengths of this particular study revolve around the cohort of soreness measures and hemodynamic markers that contribute a more comprehensive analysis to the existing body of published literature. Some of the more recent endurance-based tart cherry supplementation research studies have investigated phytonutrient effectiveness on a comprehensive panel of hemodynamic markers, which will allow for parallels to be drawn to the powdered tart cherry supplement used in the current study. The current study did not enter the study cohort into a previously established race competition, but rather created a half-marathon race exclusively for the study that started and ended near the laboratory building for convenient and consistent testing surrounding the race. The

utilization of this supplement within a trained population demonstrated its effectiveness under normative training, diet, and performance conditions. Subject compliance with supplementation was likely enhanced over past tart cherry supplement studies due to the simplicity of encapsulated powdered supplement versus a potentially inconvenient and/or unpalatable juice used previously. Potential limitations and weakness of the current study should also be considered. The placebo-control matched design of this study was effective in equalizing study subject exposure to the conditions of the half-marathon irrespective of supplement group. However, compared to some of the previous research implementing a cross-over design, there might have been some variability associated with subject pairing. A large portion of the study cohort were triathletes who train together on a regular basis, but VO_2 max testing was not implemented in this study design to determine aerobic capacity of each runner at the time of the study. Differences in aerobic state of training beyond the study inclusion/exclusion criteria may also have been a source of variability in the study cohort recruitment. Due to the large number of hemodynamic markers measured in this study, the five selected time points of blood draws over the course of the experimental period may have not fully represented the pharmacokinetic profile of each marker. Despite controlling 48-h training activity and NSAID intake with a 10-h fast before each session, the hydration status of each subject prior to the half-marathon was not controlled nor tested. Differences in hydration status among study subjects could have created variability in a cohort of this size. The 48-hour NSAID ingestion limitation may not

have been a sufficient washout time for all NSAID-type medications considering the large range in reported half-life of common NSAIDs (1.6 to 30-h), which may have also been a contributing source of acute variability. However, chronic or habitual NSAID users were excluded from the study pool during the initial study screening process, so the 48-h NSAID restriction was utilized as a secondary control point to help eliminate potential effects of acute NSAID ingestion and strengthen study validity. The study design could have also been improved with the incorporation of aerobic and/or muscular strength testing at each of the recovery time points to help elucidate the effect of the supplement on performance recovery in this study population. The major overriding strength of the current study is that this is the first study to be conducted utilizing a powdered form of tart cherries rather than a juice or concentrate.

Conclusion

The findings of the current study revealed that consumption of a Montmorency powdered tart cherry supplement 7-d before, the day of, and 2-d after completing an endurance running challenge, appears to be an effective dietary supplement that may help attenuate post-run markers of muscle catabolism and physiological stress in aerobically trained individuals. Attenuation of inflammatory markers over the 48-h recovery also demonstrates significant promise with powdered tart cherry supplementation. Coupled with the dampening of the inflammatory response, the powdered tart cherry runners seemed to better maintain post-run redox balance compared to placebo supplemented runners. The initial effectiveness on aerobic

performance, serum markers of muscle catabolism, physiological stress, and inflammatory mechanisms coupled with a more stable post-run redox balance potentially indicates a reduction in secondary muscle damage as a result of powdered tart cherry supplementation. Despite inconclusive evidence surrounding the perceptions of medial quadriceps soreness, the primary findings of the current study demonstrate that powdered tart cherry supplementation in endurance-trained individuals provides similar benefits as previously studied tart cherry juices or concentrates following acute bouts of aerobic-based exercise.

Future Direction of Research

Short-term supplementation with powdered tart cherries surrounding single bouts of demanding resistance and endurance exercise in trained populations has demonstrated beneficial effects in the current two studies. The results of the current two studies align closely with or exhibit more beneficial effects than previous performance research conducting utilizing tart cherry juice or concentrate ingestion. At the basic level, future research needs to directly compare short-term tart cherry juice, concentrate, and powder ingestion of equal anthocyanin content, gallic acid equivalence, and ORAC (Oxygen Radical Absorbance Capacity) surrounding a single bout of endurance or resistance exercise. Several endurance exercise modalities should be examined utilizing this type of supplementation protocol to help elucidate comparisons between previous studies, such as endurance running (e.g. half-marathon, marathon), endurance cycling, running and cycling intervals conducted on a flat grade or downhill. Further, several resistance-

based exercise modalities should be implemented as a basis for comparison between previous research such as eccentrically-resisted single leg elbow flexion and knee extension, upper body strength exercise protocol (e.g. bench press), lower body strength exercise protocol (e.g. barbell back squat), or repeated eccentrically-braked plyometrics (e.g. progressive double or single leg depth jump workout).

Expanding beyond the short-term supplementation studies surrounding a single bout of exercise, research could also be extended to longer term supplementation surrounding periods of intensive training regimens (e.g. 2-wk pre-season training, ultra-endurance competitions, or military basic training for new recruits). While there has been some previous antioxidant vitamin and phytochemical/functional food supplementation research conducted over longer periods (e.g. 4-6-wk) in both trained and untrained populations, there has not been any extended supplementation studies in the tart cherry literature. Due to limited research literature examining the combination of phytochemical/functional foods (e.g. tart cherry powder) with other recovery supplements such as amino acids and/or protein on similar, there is another future research opportunity to study measures of exercise performance, muscle, and overall physiological recovery as a result of this type of combination supplementation.

Additionally, little pharmacokinetic and pharmacodynamics research has been conducted in studies. Understanding differences in bioavailability of the active compounds within certain functional foods or beverages is crucial in determining the most beneficial supplements, ideal timetable of ingestion, and most effective

formulation. Some of the most recently published research in the clinical nutrition field has hypothesized and explored whether the active bioactive compounds exist within the food supplement or whether ingestion of certain natural supplement compounds spawn the activation of internal bioactives as a result of the digestive process. A future research direction may examine this debate with various forms of tart cherry supplementation in diseased, healthy, and exercising populations.

When examining the individual results of both the resistance and endurance studies, there is evidence that some individuals responded considerably to the supplementation whereas others did not. An interesting future research direction would compare the demographic, nutritional, performance, and physiological differences in responders versus non-responders. As a more detailed expansion of this future research, varying dosage levels of tart cherry powder could be studied to determine effects of supplementation on criteria similar to that presented in the current research coupled with effects of dosage on responders versus non-responders.

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APPENDIX A

Tart Cherry Resistance Study Consent Form

Project Title: **Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness Following Intense Resistance Exercise**

You are invited to take part in a research study being conducted by Dr. Richard Kreider, a researcher from Texas A&M University and funded by Anderson Global Group, LLC. The information in this form is provided to help you decide whether or not to take part. If you decide to take part in the study, you will be asked to sign this consent form. If you decide you do not want to participate, there will be no penalty to you, and you will not lose any benefits you normally would have.

Why Is This Study Being Done?
The purpose of this study is to determine if consumption of powdered tart cherries prior to and following intense resistance exercise will lessen the inflammatory and/or muscle damaging effects of that exercise.

Why Am I Being Asked To Be In This Study?
You are being asked to be in this study because you are an apparently healthy resistance-trained male between the ages of 18 and 40. You must have been involved in a progressive resistance-training program that included squat exercise training for at least six months prior to the initiation of this study and be able to perform a standard barbell squat in a power rack of at least 1.5 times your body weight. You will not be allowed to participate in this study if you have any metabolic disorders including known electrolyte abnormalities; heart disease, arrhythmias, diabetes, thyroid disease, or hypogonadism; a history of hypertension, hepatorenal, musculoskeletal, autoimmune, or neurologic disease; if you are taking thyroid, anti-hyperlipidemic, hypoglycemic, anti-hypertensive, anti-inflammatory, or androgenic medications; and/or any known allergies to cherries, other berries, or foods and juices containing high levels of phenolic compounds or anthocyanins (see Tables 1 and 2). If you meet eligibility criteria you will be informed of the requirements of the study and sign an informed consent statement in compliance with the Human Subject's Guidelines of Texas A&M University and the American College of Sports Medicine (ACSM).

Table 1. Phenolic compound and anthocyanin content of fruits and vegetables.

	Phenolic Compounds [Gallic Acid Equilivants (GAE)]		Total Anthocyanins	
	(mg/100g)	**(mg/4oz)***	**(mg/100g)**	**(mg/4oz)***
FRUIT				
Acai berry, raw			320 mg	358.4 mg
Apple, raw			0.6 mg	0.67 mg
Blackberry, Evergreen, raw	2-5 mg	2.2-5.6 mg	83-326 mg	93.0-365.1 mg
Blackberry, Merion, raw	3-6 mg	3.4-6.7 mg	109-317 mg	122.1-355.0 mg
Black currant, raw			130-400 mg	145.6-448.0 mg
Blood orange, raw			200 mg	224.0 mg
Blueberry, raw	315-1291 mg	352.8-1445.9 mg	25-497 mg	28.0-556.6 mg
Boysenberry, raw	6-9 mg	6.7-10.1 mg	120-160 mg	134.4-179.2 mg
Cherry, sweet bing, raw	**80-205 mg**	**89.6-229.6 mg**	**122-400 mg**	**136.6-448.0 mg**
Cherry, raw			**350-400 mg**	**392.0-448.0 mg**
Chokeberry, raw			200-1480 mg	224.0-1657.6 mg
Cranberry, raw			60-200 mg	67.2-224.0 mg
Elderberry, raw			450 mg	504.0 mg
Goji-WF, dried	562-1036 mg	629.4-1160.3mg		
Goji-B, dried	530-895 mg	593.6-1002.4 mg		
Grape, black, raw	372-572 mg	416.6-640.6 mg	36.7 mg	41.1 mg
Jujube, dried	595-944 mg	666.4-1057.3 mg		
Mango, puree	19.5-166.7 mg	21.8-1867 mg		
Nectarine, raw			6.8 mg	7.6 mg
Orange, raw			200 mg	224.0 mg
Peach, white peeled, raw	46-91 mg	51.5-101.9 mg	4.8 mg	5.4 mg
Plum, red, raw	69-161 mg	77.3-180.3 mg	2-71.8 mg	2.2-80.4 mg
Plum, black, raw	131-441 mg	146.7-493.9 mg	2-71.8 mg	2.2-80.4 mg
Prune, dried	337-399 mg	377.4-446.9 mg		
Raspberry, red, raw	163-393 mg	182.6-440.2 mg	11-390 mg	12.3-436.8 mg
Raspberry, black, raw	9.8 mg	11.0 mg	5.9 mg	6.6 mg
Red currant			80-420 mg	89.6-470.4 mg
Red grape, raw			30-750 mg	33.6-840.0 mg
Strawberry, organic, raw	159-282 mg	178.1-315.8 mg	15-75 mg	16.8-84.0 mg
VEGETABLES				
Eggplant (aubergine), raw			85.7-750 mg	96.0-84.0 mg
Cabbage, red, raw	1107 mg	1239.8 mg	322 mg	360.6 mg
Kale, raw	3689 mg	4131.7 mg		
Lettuce, red leaf, raw			2.2 mg	2.5 mg
Red raddish, raw			100 mg	112.0 mg
Radish, raw			11-60 mg	12.3 mg-67.2 mg
Red onion, raw			13-25 mg	14.6-28.0 mg
Onion, raw			7-21 mg	7.8-23.5 mg
Bean, black, raw			44.5 mg	49.8 mg

Shallots, raw	2528 mg	2831.4 mg		
Spinach, raw	7167 mg	8027.0 mg		
Swamp cabbage, raw	4175 mg	4676.0 mg		
Purple corn, raw			1642 mg	1839.0 mg

***** Normal serving size***

Table 2. Phenolic compound and total anthocyanin content of fruit and vegetable juices.

	Phenolic Compounds [Gallic Acid Equilivants (GAE)]		Total Anthocyanins	
	(mg/100 mL)	**(mg/240 mL)***	**(mg/240 mL)***	**(mg/L)**
JUICE				
Red wine			0.24-8.4 mg	1-35 mg/L
Acai + Lime juice	338-1227 mg	811-2945 mg		
Acai-I juice	315-858 mg	756-2059 mg		
Acai-M juice	276-495 mg	662-1188 mg		
Acai-Z juice	114-395 mg	274-948 mg		
Berry boost juice	172-283 mg	413-679 mg		
Black currant juice	115-261 mg	276-626 mg		
Black currant nectar, organic	70-120 mg	168-288 mg		
Blood orange juice, fresh squeeze	129-295 mg	310-708 mg	0.72-2.4 mg	3-10 mg/L
Montmorency tart cherry juice			**2188 mg**	**9117 mg/L**
Blackberry fruit juice			276 mg	1150 mg/L
Blueberry fruit juice			198-1008 mg	825-4200 mg/L
Grape, red fruit juice			72-180 mg	300-750 mg/L
Cherry, sweet fruit juice			**4.8-1080 mg**	**20-4500 mg/L**
Strawberry fruit juice			36-84 mg	150-350 mg/L
Cranberry fruit juice			144-480 mg	600-2000 mg/L
Pomegranate juice, fresh extract	142-168 mg	341-403 mg		
Chicha juice (purple corn drink)	144-501 mg	346-1202 mg		

***** Normal serving size***

How Many People Will Be Asked To Be In This Study?

Approximately 20 people will be invited to participate in this study locally.

What Are the Alternatives to being in this study?

The alternative to being in the study is not to participate.

What Will I Be Asked To Do In This Study?

You will be asked to not exercise for 48 hours nor eat or drink calorie containing drinks for 12 hours before the 3rd, 4th and 5th testing sessions/visits. You will also be asked to record all food and drink you eat and drink on food record forms for four days (including

one weekend day) prior to the baseline testing session/visit. Your participation in this study will last up to approximately ten days and include five visits (visit 1 ~ 1 hour/visit 2 ~ 1 hour/visit 3 ~ 2 hours/visit 4 and 5 ~ 30 min.). These visits are detailed below and in Table 3.

Visit 1 (Week one) – Familiarization and Entry

This visit will last about one hour. During this visit the details of the study will be explained, human subject consent forms will be signed, personal and medical history information will be completed, and you will have a general physical that will include measurement of fasting blood to determine if you can participate in the study. You will donate approximately 5 ml (about 1 teaspoon) of fasting blood from a vein in your arm according to standard procedures. You will be asked to restrict taking any non-steroidal anti-inflammatory drugs (NSAID) 48 hours prior to testing and during recovery. You will also have your height and weight measured.

Visit 2 (Day 0) – Baseline assessments

This visit will last about one hour. During this visit you will first have your height and weight measured. You will then have your body composition determined using a Dual Energy X-ray Absorptiometry (DEXA) machine. This will involve lying down on your back on the DEXA exam table in a pair of shorts or gown for about six minutes. A low dose of radiation will scan your body to determine the amount of fat weight, muscle weight, and bone weight. You will then warm-up on an isokinetic knee extension dynamometer (3 sets of 5 repetitions) at about half of your estimated one repetition maximum weight using your dominant leg followed by determination of three maximal voluntary contractions (MVC) on your dominant leg. After 5 minutes of recovery you will then warm-up performing 3 sets of 5 repetitions at 50% of your anticipated one repetition maximum (1 RM) on the back squat performed in a power rack and have 1 RM determined using standard procedures. You will then be asked to record all food ingestion on food record forms for four days and asked to not eat or drink for 12 hours and abstain from exercise and consumption of non-steroidal anti-inflammatory medications (NSAIDS) for 48 hours prior to the start of the study or visit 3.

Visit 3 (Day 8) – Pre-exercise, exercise and 60 minutes post-exercise

This visit will last about two hours. During this visit you will first donate approximately 20 ml (4 teaspoons) of blood using standard clinical procedures and rate perceptions to a standardized application of pressure using an algometer on your dominant thigh at 3 designated locations using a 10 point visual analogue scale to assess muscle soreness/tenderness. You will then warm-up and perform 3 sets of 5 repetitions at 50% of MVC of dominate knee extension/flexion with 1 minute recovery between sets followed by performing 3 MVC's on the dominant leg. You will then rest for 5 minutes and perform 1 warm-up set of 10 repetitions at 50% of 1 RM on the back squat. After a 3 minute recovery you will perform 10 sets of 10 repetitions at 50% of 1 RM on the back

squat. After a 3 minute recovery you will perform 10 sets of 10 repetitions at 70% of 1 RM with 3 minutes recovery between sets. A Tendo unit will be attached to the bar to determine peak power, average force, and total work for each repetition performed. If necessary the weight will be reduced so that you can complete 10 repetitions for each set. After a 60 minute recovery a blood sample, VAS ratings of muscle soreness to a standardized amount of pressure and 3 isokinetic knee extension MVC's will be taken on the dominant leg.

Visit 4 (Day 9) – 24 hour post-exercise

This visit will last about 30 minutes. During this visit you will first donate approximately 20 ml (4 teaspoons) of blood using standard clinical procedures. Next VAS ratings of muscle soreness to a standardized amount of pressure and 3 isokinetic knee extension MVC's will be taken on the dominant leg.

Visit 5 (Day 10) – 48 hour post-exercise

This visit will last about 30 minutes. During this visit you will first donate approximately 20 ml (4 teaspoons) of blood using standard clinical procedures. Next VAS ratings of muscle soreness to a standardized amount of pressure and 3 isokinetic knee extension MVC's will be taken on the dominant leg.

Supplementation

You will be matched into one of two groups according to age, body weight, and fat free mass. You will then be randomly assigned to ingest in a double blind manner capsules containing a placebo or powdered tart cherries. You will be asked to ingest the supplements with breakfast at 8:00 a.m. for 7 days prior to performing the exercise tests, the day of the testing, and for 2 days following testing (10 total days). The supplements will contain 480 mg of freeze dried Montmorency tart cherry skin powder derived from tart cherry skins obtained after juicing (*CherryPURE™ Tart Cherry Powder, Shoreline fruit, LLC, Traverse City, MI*).

You may be removed from the study by the investigator for these reasons:

- You do not show up for your scheduled testing sessions/visits and the investigators are unable to contact you to reschedule.
- The investigators are unable to obtain a blood sample from you.
- You do not follow your assigned supplementation protocol

Table 3. Overview of Study 1 - Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance Exercise

Visit 1: Familiarization and Entry (FAM)	*Visit 2:* Baseline Assessment (BASE)	*Visit 3:* Exercise Testing Session (T1)			*Visit 4:* 24-HR Post-Exercise (T2)	*Visit 5:* 48-HR Post-Exercise (T3)
		Pre-Exercise	Exercise Stimulus	60-MIN Post-Exercise		
Familiarization session Informed Consent Form Demographic Form Health History Form Exercise Training History Form Fasting Blood Sample General Physical Exam to Determine Qualifications to Participate in Study Restrict training and NSAID intake from 48-hrs prior to testing and during recovery	Determination of Height, Body Weight, Body Composition Isokinetic 3 MVC Isotonic Squat 1RM Start 4-day Dietary History Randomization into 2 Groups Instructions for Supplementation Supplementation Begins (480 mg of freeze dried tart cherry skins taken orally with breakfast)	Fasting Blood Sample VAS pain rating to standardized pressure application Isokinetic 3 MVC Test	Isotonic Squat Exercise (10 reps x 10 sets @ ~70% 1RM)	Blood Sample VAS pain rating to standardized pressure application Isokinetic 3 MVC Test	Fasting Blood Sample VAS pain rating to standardized pressure application Isokinetic 3 MVC Test	Fasting Blood Sample VAS pain rating to standardized pressure application Isokinetic 3 MVC Test

Are There Any Risks To Me?

The things that you will be doing are greater than risks that you would come across in everyday life. Although the researchers have tried to avoid risks, you may feel that some questions/procedures that are asked of you will be stressful or upsetting. You do not have to answer anything you do not want to. You will be exposed to a low level of radiation during the DEXA body composition test, which is similar to the amount of natural background radiation you would receive in one month while living in College Station Texas. The use of the DEXA analyzer has been shown to be a safe method of

measuring body composition and is approved by the FDA. You will donate approximately 5 ml (about 1 teaspoon) of blood during the initial familiarization/screening visit and then approximately 20 ml (about 4 teaspoons) four additional times throughout the duration of the study (twice during the testing session and once 24 hours post exercise and once 48 hours post exercise) using standard procedures. These procedures may cause a small amount of pain when the needle is inserted into the vein as well as some bleeding and bruising. You may also experience some dizziness, nausea, and/or faint if you are unaccustomed to having blood drawn. The exercise tests that will be performed may cause symptoms of fatigue, shortness of breath, and/or muscular fatigue/discomfort. The exercise tests may also cause short-term muscle soreness and moderate fatigue for several days following the tests. You may also experience muscle strains/pulls during the exercise testing and/or training program. However, exercise sessions will be conducted by trained personnel and monitored to ensure you follow appropriate exercise guidelines. The likelihood of any of these occurring is slim.

Are There Any Benefits To Me?
The direct benefit to you being in this study is to know more about your health and fitness status from the tests to be performed. However, even if no individual benefit is obtained, you will be paid for your participation.

Will There Be Any Costs To Me?
Aside from your time, there are no costs for taking part in the study.

Will I Have To Pay Anything If I Get Hurt In This Study?
If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Dr. Richard Kreider at 979-845-1333. You will not give up any of your legal rights by signing this consent form.

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in the “Are there any risks to me?” section of this consent form. However, side effects that are not currently known may happen and require care. You do not give up any of your legal rights by signing this form.

Will I Be Paid To Be In This Study?
You will receive a total of $100 ($20 for the Familiarization and $20 for each of the additional four testing sessions) in one check at the end of the study. Payment will occur after finishing all five sessions and after all study materials (food records, etc.) have

been turned in to the study staff. You will be paid on a prorated basis if you are unable to complete the entire study.

Will Information From This Study Be Kept Private?
The records of this study will be kept private. No identifiers linking you to this study will be included in any sort of report that might be published. Research records will be stored securely and only Exercise & Sport Nutrition Laboratory staff will have access to the records.

Information about you will be stored in locked file cabinets in a locked file room in an ID card swipe access controlled laboratory. Computer files will be protected with a password. This consent form will be filed securely in an official area. People who have access to your information include the Principal Investigator and research study personnel. Representatives of regulatory agencies such as the Office of Human Research Protections (OHRP) and entities such as the Texas A&M University Human Subjects Protection Program (HSPP) may access your records to make sure the study is being run correctly and that information is collected properly.

The agency that is funding this study (Anderson Global Group, LLC) and the institutions(s) where study procedures are being performed (Texas A&M University) may also see your information. However, any information that is sent to them will be coded with a number so that they cannot tell who you are. Representatives from these entities can see information that has your name on it if they come to the study site to view records. If there are any reports about this study, your name will not be in them.

Information about and related to this study will be kept confidential to the extent permitted or required by law.

Who may I Contact for More Information?
You may contact the Principal Investigator, Richard Kreider, PhD, to tell him about a concern or complaint about this research at 979-845-1333 or rkreider@hlkn.tamu.edu. You may also contact the Co-Investigator/Laboratory Research Associate, Chris Rasmussen, at 979-458-1741 or crasmussen@hlkn.tamu.edu.

For questions about your rights as a research participant; or if you have questions, complaints, or concerns about the research, you may call the Texas A&M University Human Subjects Protection Program office at (979) 458-4067 or irb@tamu.edu.

What if I Change My Mind About Participating?
This research is voluntary and you have the choice whether or not to be in this research study. You may decide to not begin or to stop participating at any time. If you choose not to be in this study or stop being in the study, there will be no effect on your student

status, medical care, employment, evaluation, relationship with Texas A&M University, etc. Any new information discovered about the research will be provided to you. This information could affect your willingness to continue your participation

STATEMENT OF CONSENT

I agree to be in this study and know that I am not giving up any legal rights by signing this form. The procedures, risks, and benefits have been explained to me, and my questions have been answered. I know that new information about this research study will be provided to me as it becomes available and that the researcher will tell me if I must be removed from the study. I can ask more questions if I want. A copy of this entire consent form will be given to me.

______________________________	______________________________
Participant's Signature	Date
______________________________	______________________________
Printed Name	Date

INVESTIGATOR'S AFFIDAVIT:

Either I have or my agent has carefully explained to the participant the nature of the above project. I hereby certify that to the best of my knowledge the person who signed this consent form was informed of the nature, demands, benefits, and risks involved in his/her participation.

______________________________	______________________________
Signature of Presenter	Date
______________________________	______________________________
Printed Name	Date

Tart Cherry Endurance Study Consent Form

Project Title: **Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage and Muscle Soreness Following Endurance Running**

You are invited to take part in a research study being conducted by Dr. Richard Kreider, a researcher from Texas A&M University and funded by Anderson Global Group, LLC. The information in this form is provided to help you decide whether or not to take part. If you decide to take part in the study, you will be asked to sign this consent form. If you decide you do not want to participate, there will be no penalty to you, and you will not lose any benefits you normally would have.

Why Is This Study Being Done?

The purpose of this study is to determine if consumption of powdered tart cherries prior to and following intense endurance exercise will lessen the inflammatory and/or muscle damaging effects of that exercise.

Why Am I Being Asked To Be In This Study?

You are being asked to be in this study because you are an apparently healthy male or female runner or triathlete between the ages of 18 and 40. You must have been involved in a consistent running program for at least one year and be able to run 13.1 miles in less than 2 hours. You will not be allowed to participant in this study if you have any metabolic disorders including known electrolyte abnormalities; heart disease, arrhythmias, diabetes, thyroid disease, or hypogonadism; a history of hypertension, hepatorenal, musculoskeletal, autoimmune, or neurologic disease; if you are taking thyroid, anti-hyperlipidemic, hypoglycemic, anti-hypertensive, anti-inflammatory, or androgenic medication; and/or any known allergies to cherries, other berries, or foods and juices containing high levels of phenolic compounds or anthocyanins (see Tables 1 and 2). If you meet eligibility criteria you will be informed of the requirements of the study and sign an informed consent statement in compliance with the Human Subject's Guidelines of Texas A&M University and the American College of Sports Medicine (ACSM).

Table 1. Phenolic compound and anthocyanin content of fruits and vegetables.

	Phenolic Compounds [Gallic Acid Equilivants (GAE)]		Total Anthocyanins	
	(mg/100g)	(mg/4oz)*	(mg/100g)	(mg/4oz)*
FRUIT				
Acai berry, raw			320 mg	358.4 mg
Apple, raw			0.6 mg	0.67 mg
Blackberry, Evergreen, raw	2-5 mg	2.2-5.6 mg	83-326 mg	93.0-365.1 mg
Blackberry, Merion, raw	3-6 mg	3.4-6.7 mg	109-317 mg	122.1-355.0 mg
Black currant, raw			130-400 mg	145.6-448.0 mg
Blood orange, raw			200 mg	224.0 mg
Blueberry, raw	315-1291 mg	352.8-1445.9 mg	25-497 mg	28.0-556.6 mg
Boysenberry, raw	6-9 mg	6.7-10.1 mg	120-160 mg	134.4-179.2 mg
Cherry, sweet bing, raw	**80-205 mg**	**89.6-229.6 mg**	**122-400 mg**	**136.6-448.0 mg**
Cherry, raw			**350-400 mg**	**392.0-448.0 mg**
Chokeberry, raw			200-1480 mg	224.0-1657.6 mg
Cranberry, raw			60-200 mg	67.2-224.0 mg
Elderberry, raw			450 mg	504.0 mg
Goji-WF, dried	562-1036 mg	629.4-1160.3mg		
Goji-B, dried	530-895 mg	593.6-1002.4 mg		
Grape, black, raw	372-572 mg	416.6-640.6 mg	36.7 mg	41.1 mg
Jujube, dried	595-944 mg	666.4-1057.3 mg		
Mango, puree	19.5-166.7 mg	21.8-1867 mg		
Nectarine, raw			6.8 mg	7.6 mg
Orange, raw			200 mg	224.0 mg
Peach, white peeled, raw	46-91 mg	51.5-101.9 mg	4.8 mg	5.4 mg
Plum, red, raw	69-161 mg	77.3-180.3 mg	2-71.8 mg	2.2-80.4 mg
Plum, black, raw	131-441 mg	146.7-493.9 mg	2-71.8 mg	2.2-80.4 mg
Prune, dried	337-399 mg	377.4-446.9 mg		
Raspberry, red, raw	163-393 mg	182.6-440.2 mg	11-390 mg	12.3-436.8 mg
Raspberry, black, raw	9.8 mg	11.0 mg	5.9 mg	6.6 mg
Red currant			80-420 mg	89.6-470.4 mg
Red grape, raw			30-750 mg	33.6-840.0 mg
Strawberry, organic, raw	159-282 mg	178.1-315.8 mg	15-75 mg	16.8-84.0 mg
VEGETABLES				
Eggplant (aubergine), raw			85.7-750 mg	96.0-84.0 mg
Cabbage, red, raw	1107 mg	1239.8 mg	322 mg	360.6 mg
Kale, raw	3689 mg	4131.7 mg		
Lettuce, red leaf, raw			2.2 mg	2.5 mg
Red raddish, raw			100 mg	112.0 mg
Radish, raw			11-60 mg	12.3 mg-67.2 mg
Red onion, raw			13-25 mg	14.6-28.0 mg
Onion, raw			7-21 mg	7.8-23.5 mg

Bean, black, raw			44.5 mg	49.8 mg
Shallots, raw	2528 mg	2831.4 mg		
Spinach, raw	7167 mg	8027.0 mg		
Swamp cabbage, raw	4175 mg	4676.0 mg		
Purple corn, raw			1642 mg	1839.0 mg

**** Normal serving size***

Table 2. Phenolic compound and total anthocyanin content of fruit and vegetable juices.

	Phenolic Compounds [Gallic Acid Equilivants (GAE)]		Total Anthocyanins	
	(mg/100 mL)	**(mg/240 mL)***	**(mg/240 mL)***	**(mg/L)**
JUICE				
Red wine			0.24-8.4 mg	1-35 mg/L
Acai + Lime juice	338-1227 mg	811-2945 mg		
Acai-I juice	315-858 mg	756-2059 mg		
Acai-M juice	276-495 mg	662-1188 mg		
Acai-Z juice	114-395 mg	274-948 mg		
Berry boost juice	172-283 mg	413-679 mg		
Black currant juice	115-261 mg	276-626 mg		
Black currant nectar, organic	70-120 mg	168-288 mg		
Blood orange juice, fresh squeeze	129-295 mg	310-708 mg	0.72-2.4 mg	3-10 mg/L
Montmorency tart cherry juice			**2188 mg**	**9117 mg/L**
Blackberry fruit juice			276 mg	1150 mg/L
Blueberry fruit juice			198-1008 mg	825-4200 mg/L
Grape, red fruit juice			72-180 mg	300-750 mg/L
Cherry, sweet fruit juice			**4.8-1080 mg**	**20-4500 mg/L**
Strawberry fruit juice			36-84 mg	150-350 mg/L
Cranberry fruit juice			144-480 mg	600-2000 mg/L
Pomegranate juice, fresh extract	142-168 mg	341-403 mg		
Chicha juice (purple corn drink)	144-501 mg	346-1202 mg		

**** Normal serving size***

How Many People Will Be Asked To Be In This Study?

Approximately 30 people will be invited to participate in this study locally.

What Are the Alternatives to being in this study?

The alternative to being in the study is not to participate.

What Will I Be Asked To Do In This Study?

You will be asked to not exercise for 48 hours nor eat or drink calorie containing drinks for 12 hours before the 3rd, 4th and 5th testing sessions/visits. You will also be asked to

record all food and drink you eat and drink on food record forms for four days (including one weekend day) prior to the exercise testing session/visit. Your participation in this study will last up to approximately ten days and include five visits (visit 1 ~ 1 hour/visit 2 ~ 1 hour/visit 3 ~ 3 hours/visit 4 and 5 ~ 30 min.). These visits are detailed below and in Table 3.

Visit 1 (Week one) – Familiarization and entry
This visit will last about one hour. During this visit the details of the study will be explained, human subject consent forms will be signed, personal and medical history information will be completed, and you will have a general physical that will include measurement of fasting blood to determine if you can participate in the study. You will donate approximately 5 ml (about 1 teaspoon) of fasting blood from a vein in your arm according to standard procedures. You will be asked to restrict taking any non-steroidal anti-inflammatory drugs (NSAID) 48 hours prior to testing and during recovery. You will also have your height and weight measured.

Visit 2 (Day 0) – Baseline assessments
This visit will last about one hour. During this visit you will first have your height and weight measured. You will then have your body composition determined using a Dual Energy X-ray Absorptiometry (DEXA) machine. This will involve lying down on your back on the DEXA exam table in a pair of shorts or gown for about six minutes. A low dose of radiation will scan your body to determine the amount of fat weight, muscle weight, and bone weight. You will then be asked to record all food ingestion on food record forms for four days and asked to not eat or drink for 12 hours and abstain from exercise and consumption of non-steroidal anti-inflammatory medications (NSAIDS) for 48 hours prior to the start of the study or visit 3.

Visit 3 (Day 8) – Pre-exercise, exercise and 60 minutes post-exercise
This visit will last about three hours. During this visit you will first donate approximately 20 ml (4 teaspoons) of blood using standard clinical procedures and rate perceptions to a standardized application of pressure using an algometer on your dominant thigh at 3 designated locations using a 10 point visual analogue scale to assess muscle soreness/tenderness. You will then be asked to warm-up as you normally would before running a road race. The race will be conducted on campus and around the ESNL. You will then be asked to run a 13.1 mile run outdoors at your normal race/competition pace. You will be provided a standard amount of a glucose-electrolyte drink at regular intervals during the run. After a 60 minute recovery a blood sample and VAS ratings of muscle soreness to a standardized amount of pressure will be taken.

Visit 4 (Day 9) – 24 hour post-exercise

This visit will last about 30 minutes. During this visit you will first donate approximately 20 ml (4 teaspoons) of blood using standard clinical procedures. Next VAS ratings of muscle soreness to a standardized amount of pressure will be taken.

Visit 5 (Day 10) – 48 hour post-exercise

This visit will last about 30 minutes. During this visit you will first donate approximately 20 ml (4 teaspoons) of blood using standard clinical procedures. Next VAS ratings of muscle soreness to a standardized amount of pressure will be taken.

Supplementation

You will be matched into one of two groups according to age, body weight, and fat free mass. You will then be randomly assigned to ingest in a double blind manner capsules containing a placebo or powdered tart cherries. You will be asked to ingest the supplements with breakfast at 8:00 a.m. for 7 days prior to performing the exercise test, the day of the testing, and for 2 days following testing (10 total days). The supplements will contain 480 mg of freeze dried Montmorency tart cherry skin powder derived from tart cherry skins obtained after juicing (*CherryPURE™ Tart Cherry Powder, Shoreline fruit, LLC, Traverse City, MI*).

You may be removed from the study by the investigator for these reasons:

- You do not show up for your scheduled testing sessions/visits and the investigators are unable to contact you to reschedule.
- The investigators are unable to obtain a blood sample from you.
- You do not follow your assigned supplementation protocol.

Table 3. Overview of Study - Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Endurance Exercise

Visit 1: Familiarization and Entry (FAM)	*Visit 2:* Baseline Assessment (BASE)	*Visit 3:* Exercise Testing Session (T1)			*Visit 4:* 24-HR Post-Exercise (T2)	*Visit 5:* 48-HR Post-Exercise (T3)
		Pre-Exercise	Exercise Stimulus	60-MIN Post-Exercise		
Familiarization session Informed Consent Form Demographic Form Health History Form Exercise Training History Form Fasting Blood Sample General Physical Exam to Determine Qualifications to Participate in Study Restrict training and NSAID intake from 48-hrs prior to testing and during recovery	Determination of Height, Body Weight, Body Composition Start 4-day Dietary History Randomization into 2 Groups Instructions for Supplementation Supplementation Begins (480 mg of freeze dried tart cherry skins taken orally with breakfast)	Fasting Blood Sample VAS pain rating to standardized pressure application	13.1 mile outdoor run	Blood Sample VAS pain rating to standardized pressure application	Fasting Blood Sample VAS pain rating to standardized pressure application	Fasting Blood Sample VAS pain rating to standardized pressure application

Are There Any Risks To Me?

The things that you will be doing are greater than risks than you would come across in everyday life. Although the researchers have tried to avoid risks, you may feel that some questions/procedures that are asked of you will be stressful or upsetting. You do not have to answer anything you do not want to. You will be exposed to a low level of radiation during the DEXA body composition test, which is similar to the amount of

natural background radiation you would receive in one month while living in College Station Texas. The use of the DEXA analyzer has been shown to be a safe method of measuring body composition and is approved by the FDA. You will donate approximately 5 ml (about 1 teaspoon) of blood during the initial familiarization/screening visit and then approximately 20 ml (about 4 teaspoons) four additional times throughout the duration of the study (twice during the testing session and once 24 hours post exercise and once 48 hours post exercise) using standard procedures. These procedures may cause a small amount of pain when the needle is inserted into the vein as well as some bleeding and bruising. You may also experience some dizziness, nausea, and/or faint if you are unaccustomed to having blood drawn. The exercise test that will be performed may cause symptoms of fatigue, shortness of breath, and/or muscular fatigue/discomfort. The exercise test may also cause short-term muscle soreness and moderate fatigue for several days following the test. You may also experience muscle strains/pulls during the exercise testing and/or training program. However, exercise sessions will be conducted by trained personnel and monitored to ensure you follow appropriate exercise guidelines. The likelihood of any of these occurring is slim.

Are There Any Benefits To Me?

The direct benefit to you by being in this study is to know more about your health and fitness status from the tests to be performed. However, even if no individual benefit is obtained, you will be paid for your participation.

Will There Be Any Costs To Me?

Aside from your time, there are no costs for taking part in the study.

Will I Have To Pay Anything If I Get Hurt In This Study?

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Dr. Richard Kreider at 979-845-1333. You will not give up any of your legal rights by signing this consent form.

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in the “Are there any risks to me?” section of this consent form. However, side effects that are not currently known may happen and require care. You do not give up any of your legal rights by signing this form.

Will I Be Paid To Be In This Study?

You will receive a total of $100 ($20 for the Familiarization and $20 for each of the additional four testing sessions) in one check at the end of the study. Payment will occur

after finishing all testing sessions and after all study materials (food records, etc.) have been turned in to the study staff. You will be paid on a prorated basis if you are unable to complete the entire study.

Will Information From This Study Be Kept Private?
The records of this study will be kept private. No identifiers linking you to this study will be included in any sort of report that might be published. Research records will be stored securely and only Exercise & Sport Nutrition Laboratory staff will have access to the records.

Information about you will be stored in locked file cabinets in a locked file room in an ID card swipe access controlled laboratory. Computer files will be protected with a password. This consent form will be filed securely in an official area.

People who have access to your information include the Principal Investigator and research study personnel. Representatives of regulatory agencies such as the Office of Human Research Protections (OHRP) and entities such as the Texas A&M University Human Subjects Protection Program (HSPP) may access your records to make sure the study is being run correctly and that information is collected properly.

The agency that is funding this study (Anderson Global Group, LLC) and the institutions(s) where study procedures are being performed (Texas A&M University) may also see your information. However, any information that is sent to them will be coded with a number so that they cannot tell who you are. Representatives from these entities can see information that has your name on it if they come to the study site to view records. If there are any reports about this study, your name will not be on them.

Information about you and related to this study will be kept confidential to the extent permitted or required by law.

Who may I Contact for More Information?
You may contact the Principal Investigator, Richard Kreider, PhD, to tell him about a concern or complaint about this research at 979-845-1333 or rkreider@hlkn.tamu.edu. You may also contact the Co-Investigator/Laboratory Research Associate, Chris Rasmussen, at 979-458-1741 or crasmussen@hlkn.tamu.edu.

For questions about your rights as a research participant; or if you have questions, complaints, or concerns about the research, you may call the Texas A&M University Human Subjects Protection Program office at (979) 458-4067 or irb@tamu.edu.

What if I Change My Mind About Participating?
This research is voluntary and you have the choice whether or not to be in this research

study. You may decide to not begin or to stop participating at any time. If you choose not to be in this study or stop being in the study, there will be no effect on your student status, medical care, employment, evaluation, relationship with Texas A&M University, etc. Any new information discovered about the research will be provided to you. This information could affect your willingness to continue your participation.

STATEMENT OF CONSENT

I agree to be in this study and know that I am not giving up any legal rights by signing this form. The procedures, risks, and benefits have been explained to me, and my questions have been answered. I know that new information about this research study will be provided to me as it becomes available and that the researcher will tell me if I must be removed from the study. I can ask more questions if I want. A copy of this entire consent form will be given to me.

______________________________	______________________________
Participant's Signature	Date
______________________________	______________________________
Printed Name	Date

INVESTIGATOR'S AFFIDAVIT:

Either I have or my agent has carefully explained to the participant the nature of the above project. I hereby certify that to the best of my knowledge the person who signed this consent form was informed of the nature, demands, benefits, and risks involved in his/her participation.

______________________________	______________________________
Signature of Presenter	Date
______________________________	______________________________
Printed Name	Date

APPENDIX B

Tart Cherry Research Medical History Questionnaire

Title Page

Pg | 1 | of | 6 |

General Screening Form

Study:____________________ **IRB:** _______________

Texas A&M, College Station, TX

Screening# [ ][ ][ ]

Subject Initials [ ]

Consent Date [ ][ ] mm [ ][ ] dd [ ][ ][ ][ ] yyyy

Screening Date [ ][ ] mm [ ][ ] dd [ ][ ][ ][ ] yyyy

Subject ID [ ]

Personal Data

Pg | 2 | of | 6

Visit: FAM   Screening #: | |

Name: ____________________

Address: ____________________

Phone #: ____________________

E-mail: ____________________

Local PCP: ____________________ ☐ None

____

Demographics

Pg 3 of 6

Visit: FAM **Screening #:**

Sex: ☐ M ☐ F

DOB: ☐☐ (mm) ☐☐ (dd) ☐☐☐☐ (yyyy) Age at enrollment: ______ y

Race:
(Mark all which apply)

- ☐ White
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ Asian
- ☐ American Indian/Alaska Native
- ☐ Unknown

Ethnicity:
(Mark only 1)

- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown

General Health & Physical Exam

Visit: FAM **Screening #:**

PMHx: ______

Surgical Hx: ______

Allergies and drug reactions: ______

Medications:

SHx: Lives with: ______ Where: ______

Occupation Hx: ______

Smoking: Duration: ______ PPD x ______ Yrs EtOH: ______
Former smoker: when stopped: ______ Duration: ______ PPD x ___ Yrs

Vital signs:

HR: ______ m T: ______ . ___ ___ °C ___ °F

BP: ______ / ______ mmHg SaO2: ______ %

Anthropometry:

Height: ______ . ___ cm Weight: ______ . ___ kg BMI: ______ . ___ kg/m2

______ . ___ in ______ . ___ lbs

General Health & Physical Exam

Visit: FAM **Screening #:**

ROS: fever chills sweats wtΔ fatigue appetite sleep
Skin: itching rash sores susp. moles/lesions- healing recentΔ
Head: dizzy fainting HA/LOC trauma
Eyes: correction Δvision-double tearing itching/redness
Ears: Δhearing ringing earache vertigo/tinnitus
Nose: epistaxis rhinorrhea allergies
Mouth/Throat: bleeding gums sore mouth/throat swollen neck
CV: angina palpitations DOE orthopnea/PND edema
Pulm: SOB wheeze cough hemoptysis TB
Hematologic: bruise /bleed easily transfusion hx
GI: dysphagia N / V abd pain GERD hematochezia jaundice
GU: freq urgency hesitancy dys- hematuria incont UTI's stones
Genital: testicular masses hernias
Endocrine: polyuria polydipsia skin/hair ? thyroid hx
Vascular: claudication DVT hx
MSK: jt pain stiffness arthritis gout
Neuro: numbness weakness/atrophy seizure/tremor
Psych: depression anxiety recent memoryΔ
Female: regular dysmenorrhea pregnancies menopause
Breast: skinΔ lumps pain discharge

PE: Gen: Well
Skin: cap refill: no rash lesions:
Head: no trauma no bruising no masses
Eyes: PERRLA EOMI no ptosis sclera clear
Ears: good acuity TM: nl reflex/intact
Nose: nl
Mouth/Throat: nl/pink, moist mucous membranes no lesions
Neurological: Alert & oriented×3, nl MS via conversation
Cranial Nerves: II - XII intact/nl
Motor: 5/5 UE/LE's bil
Sensation: intact LT UE/LE's
DTRs: symmetric/nl biceps knee ankle
Gait/Station: nl
Neck: no LAD no masses no bruits no JVD supple stiff
Chest: CTA bil equal expansion
Extremities: no C/C/E Major jts: no swelling full ROM
Heart: Reg no M/R/G
Pulses Bil: PT / DP: 2+
Abdomen: soft, NT/ND BS + no masses / organomegaly

General Health & Physical Exam

Visit: FAM **Screening #:** | | **Pg** 6 of 6

Assessment: ______________________________

Blood Draw: ☐ Y ☐ N ______________________________

Blood draw performed by: ______________________________

Lab Results Reviewed: ☐ Y ☐ N

Eligible based on General Health and Physical Exam: ☐ Y ☐ N

____
Signature of staff member performing exam

Date: mm | dd | yyyy

____
Signature of Principal Investigator (page 2-13)

Date: mm | dd | yyyy

APPENDIX C

Tart Cherry Research Radiation Exposure Consent Form

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trial: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness Following Endurance Running

Radiation Exposure Questionnaire for Women of Child Bearing Age

Radiation exposure may affect fetal development. Although the DEXA test will only expose you to a small amount of radiation (1.5mR per scan), you should be aware that there is a possibility that if you become pregnant during the course of the study that the x-ray exposure may be harmful to the fetus. Therefore, it is important to conduct x-ray tests within 10-14 days of the start of a female's menstrual cycle if the she is of child bearing age, sexually active, and/or is not taking birth control pills. The following questionnaire must be completed so that we know when it is an appropriate time to conduct the DEXA body composition tests. Please be assured that this information will be kept confidential within the limits permitted by law.

Current Age? ________
Age of first period? ________
Date of last period? ________
Normal length of menstrual cycle? ________
Do you use birth control pills? ________
Are you pregnant or have a desire for pregnancy? ________

Note: If you happen to get pregnant during the course of this study, you must notify research assistants so that appropriate precautions can be made.

I confirm that I have completed this questionnaire honestly and agree to notify researchers within the ESNL of any change in the length of my menstrual cycle and/or pregnancy status.

____
Participant Name

________________________________ ____________________
Participant Signature Date

________________________________ ____________________
Staff Signature Date

APPENDIX D

Tart Cherry Resistance Screening Face Sheet

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trial: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance Exercise

Demographics *ESNL Staff Initials:* _____

Name: ________________________________ Testing Session: ***Familiarization (FAM)***
Date: _____________ DOB: ___________ Age: _________

Screening Measures *ESNL Staff Initials:* _____
Psychological Questionnaires/Informed Consent:

HLKN Informed Consent: _____ Exercise Training History Form: _____
Demographic Form: _____ Health History & General Screening Form: _____
Financial Paperwork: _____ Review Medical History/Screening (CTRAL RN): _____

Physiological Parameters:

Last Meal: ______ am/pm Resting H.R.: ______ bpm
Hours Fasted: ______ hrs. Resting B.P.: ______ /______ mmHg
Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm

Baseline Assessment Measures *ESNL Staff Initials:* _____

Date: _____________ Age: _________ Testing Session: ***Baseline Assessment (BASE)***

Physiological Parameters: *ESNL Staff Initials:* _____

Height: ______ in. Weight: ______ lbs. DEXA #2: ______
Time: ______ am/pm

Exercise/Strength Parameters: *ESNL Staff Initials:* _____

Kin Com Isokinetic Testing: *Dominant Leg*: R or L (circle one)

Seat Bottom Distance (G): ______ cm Seat Track Position: ______ cm

Dynamometer Track Position: ______ cm Leg Lever Arm Length: ______ cm

Isokinetic EXT/FLEX SMVC Warm-up (3 sets x **ESTIMATED 50% MVC** x 5 reps): _______

Isokinetic EXT/FLEX MVC Determination (1 set x **MVC** x 3 reps): _______

Smith Machine Maximal Back Squat:

Foot Position: Heel Distance from Rack Front: ______ in.

Distance between Feet: ______ in.

Estimated Back Squat 1RM: _______ lbs.

50% Estimated Back Squat 1RM: _______ lbs.

Warm-up 50% 1RM (3 sets x 5 reps): _______

Preceding Weights/Reps for Back Squat 1RM Determination:

______x______: ______x______: ______x______: ______x______: ______x______

Tart Cherry Endurance Screening Face Sheet

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trial: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Endurance Running

Demographics *ESNL Staff Initials:* _____

Name: _____________________________ Testing Session: ***Familiarization (FAM)***

Date: _____________ DOB: ___________ Age: _________

Screening Measures *ESNL Staff Initials:* _____
Psychological Questionnaires/Informed Consent:

HLKN Informed Consent: _____
Demographic Form: _____
Financial Paperwork: _____
Exercise Training History Form: _____
Health History & General Screening Form: _____
Review Medical History/Screening (CTRAL RN): _____

Physiological Parameters:

Last Meal: ______ am/pm
Hours Fasted: ______ hrs.
Resting H.R.: ______ bpm
Resting B.P.: ______ /______ mmHg

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm

Baseline Assessment Measures *ESNL Staff Initials:* _____

Date: _____________ Age: _________
Testing Session: ***Baseline Assessment (BASE)***

Physiological Parameters: *ESNL Staff Initials:* _____

Height: ______ in.
Weight: ______ lbs.
DEXA #2: ______
Time: ______ am/pm

Self-Reported Endurance Capabilities: *ESNL Staff Initials:* _____

Recent Performances and Results:

1] ___________________________________ Finish Time: _________ min:sec

Average Race Pace: _________ min:sec/km OR

Average Race Pace: _________ min:sec/mi

2] ___________________________________ Finish Time: _________ min:sec

Average Race Pace: _________ min:sec/km OR

Average Race Pace: _________ min:sec/mi

Average Weekly Training Mileage: _________ miles/wk

Average/Typical Training Pace: _________ min:sec/mi

APPENDIX E

Tart Cherry Resistance Testing Face Sheet

Texas A&M University: Exercise & Sport Nutrition Laboratory

Trial: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance Exercise

Demographics *ESNL Staff Initials:* _____

Name: ________________________________ Testing Session: ***Exercise (EX)***
Date: _____________ DOB: ___________ Age: _________
Food Logs: _______

Testing Measures *ESNL Staff Initials:* _____

Physiological Parameters:
Last Meal: ______ am/pm
Hours Fasted: ______ hrs.
Last Exercise: M T W TH F SA SU (circle one)
Abstained Exercise: ______ hrs.
Abstained NSAIDs: ______ hrs.

Height: ______ in.
Weight: ______ lbs.
Resting H.R.: ______ bpm
Resting B.P.: _____ /______ mmHg

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm
Algometer GPRS Evaluation Completed: ______

Exercise/Strength Parameters: *ESNL Staff Initials:* _____

Kin Com Isokinetic Testing:
Seat Bottom Distance (G): ______ cm
Dynamometer Track Position: ______ cm

Dominant Leg: R or L (circle one)
Seat Track Position: ______ cm
Leg Lever Arm Length: ______ cm

Isokinetic EXT/FLEX 50% MVC: ________ (from Baseline Testing)
Isokinetic EXT/FLEX SMVC Warm-up (3 sets x **50% MVC** x 5 reps): _______
Isokinetic EXT/FLEX MVC (1 set x **MVC** x 3 reps): _______

Smith Machine Maximal Back Squat:

Foot Position: Heel Distance from Rack Front: ______ in.
Distance between Feet: ______ in.

Back Squat 1RM: _______ lbs.
Warm-up 50% 1RM (1 sets x 10 reps): ______

50% Back Squat 1RM: _______ lbs.
70% Back Squat 1RM: _______ lbs.

Preceding Performance Data for Back Squat Exercise 70% 1RM (10 sets x 10 reps):

SET	REPS	WEIGHT (lbs.)	PEAK POWER	AVG POWER	AVG VELOCITY
1	***1***				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
2	***1***				
	2				
	3				
	4				

	5				
	6				
	7				
	8				
	9				
	10				
3	1				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
4	1				
	2				
	3				
	4				
	5				

	6				
	7				
	8				
	9				
	10				
5	***1***				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
6	***1***				
	2				
	3				
	4				
	5				
	6				

	7				
	8				
	9				
	10				
7	1				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
8	1				
	2				
	3				
	4				
	5				
	6				
	7				

	8				
	9				
	10				
9	*1*				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
10	*1*				
	2				
	3				
	4				
	5				
	6				
	7				
	8				

	9				
	10				

Bar Displacement: ______ in. ______ cm

Recovery Measures

60 Minute Post Physiological Parameters: *ESNL Staff Initials:* _____

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm
Algometer GPRS Evaluation Completed: ______

Isokinetic EXT/FLEX SMVC Warm-up (3 sets x **50% MVC** x 5 reps): ______
Isokinetic EXT/FLEX MVC (1 set x **MVC** x 3 reps): ______

---

24 Hour Post Physiological Parameters:
Date: _____________ *ESNL Staff Initials:* _____

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm
Last Meal: ______ am/pm (Hours Fasted: ______)
Algometer GPRS Evaluation Completed: ______

Isokinetic EXT/FLEX SMVC Warm-up (3 sets x **50% MVC** x 5 reps): ______
Isokinetic EXT/FLEX MVC (1 set x **MVC** x 3 reps): ______

---

48 Hour Post Physiological Parameters:

Date: _____________ *ESNL Staff Initials:* _____

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm

Last Meal: ______ am/pm (Hours Fasted: ______)

Algometer GPRS Evaluation Completed: ______

Isokinetic EXT/FLEX SMVC Warm-up (3 sets x **50% MVC** x 5 reps): _______
Isokinetic EXT/FLEX MVC (1 set x **MVC** x 3 reps): _______

Tart Cherry Endurance Testing Face Sheet

Texas A&M University: Exercise & Sport Nutrition Laboratory

Trial: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Endurance Running

Demographics *ESNL Staff Initials:* _____

Name: ________________________________ Testing Session: ***Exercise (EX)***
Date: _____________ DOB: ___________ Age: _________ Food
Logs: _______

Testing Measures *ESNL Staff Initials:* _____

Physiological Parameters:

Last Meal: ______ am/pm Height: ______ in.
Hours Fasted: ______ hrs. Weight: ______ lbs.
Last Exercise: M T W TH F SA SU (circle one) Resting H.R.: ______ bpm
Abstained Exercise: ______ hrs. Resting B.P.: ______ /______ mmHg
Abstained NSAIDs: ______ hrs.

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube
Blood Draw Time: ______ am/pm
Algometer GPRS Evaluation Completed: ______

Exercise/Strength Parameters: *ESNL Staff Initials:* _____

Endurance Exercise Testing:

Outdoor Half Marathon (13.1 miles)
Weight: ______ lbs. Time: ________ : _________ (min:sec)
H.R.: ______ bpm Pace: ________ : _________ (min:sec/mile)

Recovery Measures

60 Minute Post Physiological Parameters: *ESNL Staff Initials:* _____

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube Blood Draw Time: ______ am/pm

Algometer GPRS Evaluation Completed: ______

---

24 Hour Post Physiological Parameters: *ESNL Staff Initials:* _____

Date: _____________

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube

Blood Draw Time: ______ am/pm

Last Meal: ______ am/pm (Hours Fasted: ______)

Algometer GPRS Evaluation Completed: ______

---

48 Hour Post Physiological Parameters: *ESNL Staff Initials:* _____

Date: _____________

Lab (ESNL/CTRAL): ______ (2) SST tubes / (1) EDTA tube

Blood Draw Time: ______ am/pm

Last Meal: ______ am/pm (Hours Fasted: ______)

Algometer GPRS Evaluation Completed: ______

APPENDIX F

Tart Cherry Research Algometer GPRS Data Sheet

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trials: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance and Endurance Exercise

Name: ______________________________ Date: ________________

PRE-EXERCISE

Algometer Graphic Pain Rating Scale (GPRS)

INSTRUCTIONS:
Please place an 'X' on the line below at the point on the line that best describes your knee pain using the following definitions as a guide:

Dull Ache: A feeling of discomfort during activity.
Slight Pain: An awareness of pain without distress.
More Slight Pain: Pain distracts attention during physical exertion.
Painful: Pain distracts attention from routine occupation such as reading & writing.
Very Painful: Pain fills the field of consciousness to the exclusion of other events.
Unbearable Pain: Comparable to the worst pain you can imagine.

Pre-Exercise Graphic Pain Rating Scale: *ESNL Staff Initials:* _____

VAS Location #1 *[¼ distance between patella and g. troch on VASTUS MEDIALIS]:*

No Pain ____ **Unbearable Pain**
Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #2 *[¼ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**
Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #3 *[½ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**
Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trials: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance and Endurance Exercise

Name: ______________________________ Date: _________________

60-MIN POST-EXERCISE

Algometer Graphic Pain Rating Scale (GPRS)

INSTRUCTIONS:
Please place an 'X' on the line below at the point on the line that best describes your knee pain using the following definitions as a guide:

Dull Ache: A feeling of discomfort during activity.
Slight Pain: An awareness of pain without distress.
More Slight Pain: Pain distracts attention during physical exertion.
Painful: Pain distracts attention from routine occupation such as reading & writing.
Very Painful: Pain fills the field of consciousness to the exclusion of other events.
Unbearable Pain: Comparable to the worst pain you can imagine.

Pre-Exercise Graphic Pain Rating Scale: *ESNL Staff Initials:* _____

VAS Location #1 *[¼ distance between patella and g. troch on VASTUS MEDIALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #2 *[¼ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #3 *[½ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trials: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance and Endurance Exercise

Name: ________________________________ Date: __________________

24-HR POST-EXERCISE

Algometer Graphic Pain Rating Scale (GPRS)

INSTRUCTIONS:
Please place an 'X' on the line below at the point on the line that best describes your knee pain using the following definitions as a guide:

Dull Ache: A feeling of discomfort during activity.
Slight Pain: An awareness of pain without distress.
More Slight Pain: Pain distracts attention during physical exertion.
Painful: Pain distracts attention from routine occupation such as reading & writing.
Very Painful: Pain fills the field of consciousness to the exclusion of other events.
Unbearable Pain: Comparable to the worst pain you can imagine.

Pre-Exercise Graphic Pain Rating Scale: *ESNL Staff Initials:* _____

VAS Location #1 *[¼ distance between patella and g. troch on VASTUS MEDIALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #2 *[¼ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #3 *[½ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trials: Effects of Tart Cherry Supplementation on Markers of Inflammation, Muscle Damage, and Muscle Soreness following Intense Resistance and Endurance Exercise

Name: ________________________________ Date: __________________

48-HR POST-EXERCISE

Algometer Graphic Pain Rating Scale (GPRS)

INSTRUCTIONS:
Please place an 'X' on the line below at the point on the line that best describes your knee pain using the following definitions as a guide:

Dull Ache: A feeling of discomfort during activity.
Slight Pain: An awareness of pain without distress.
More Slight Pain: Pain distracts attention during physical exertion.
Painful: Pain distracts attention from routine occupation such as reading & writing.
Very Painful: Pain fills the field of consciousness to the exclusion of other events.
Unbearable Pain: Comparable to the worst pain you can imagine.

Pre-Exercise Graphic Pain Rating Scale: *ESNL Staff Initials:* _____

VAS Location #1 *[¼ distance between patella and g. troch on VASTUS MEDIALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

VAS Location #2 *[¼ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

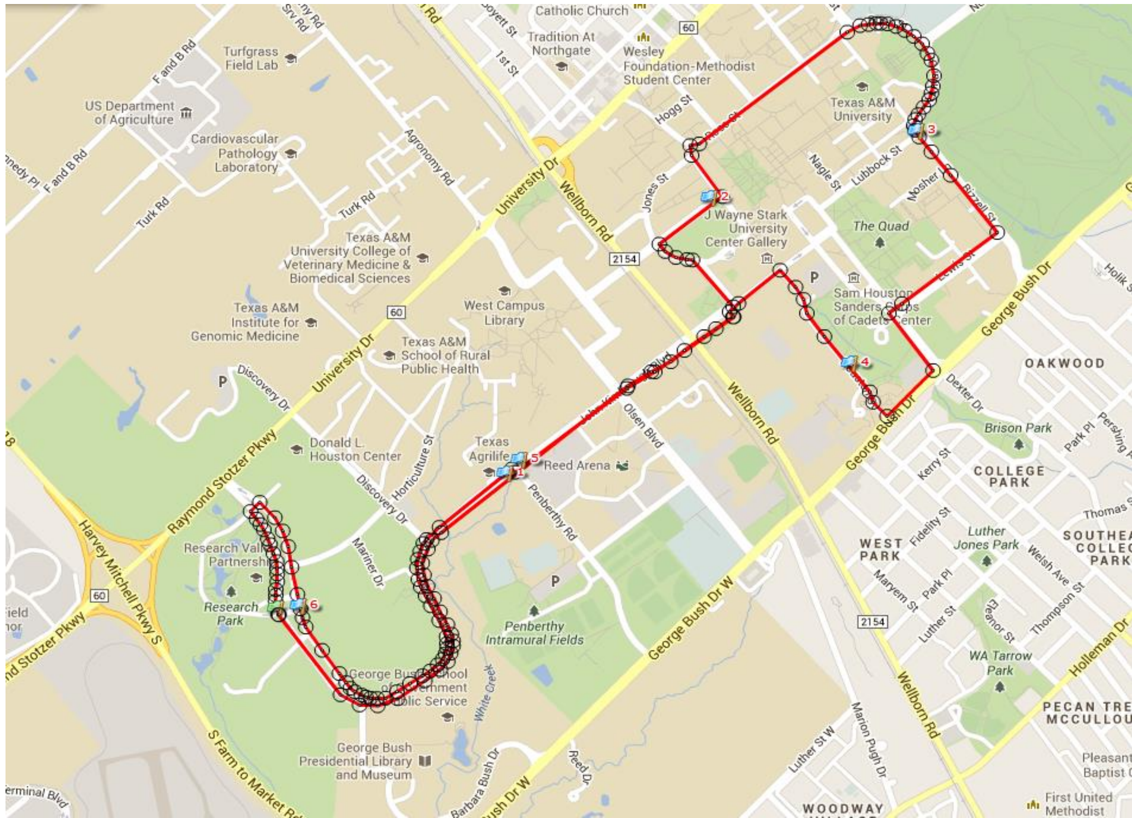
VAS Location #3 *[½ distance between patella and g. troch on VASTUS LATERALIS]:*

No Pain ____ **Unbearable Pain**

Dull Ache **Slight Pain** **More Slight Pain** **Painful** **Very Painful**

APPENDIX G

Tart Cherry Endurance Study Half Marathon Running Route



Half-Marathon Running Course = 10.55 km (6.55 mi)

Subjects completed two laps to finish half-marathon race = 21.1 km (13.1 mi) total