EFFECTS OF POLYPHENOLS SUPPLEMENTATION ON INFLAMMATION AND OXIDATIVE STRESS AFTER ACUTE EXERCISE: A SYSTEMATIC REVIEW WITH META-ANALYSIS

by

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DEDICATION

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Polyphenols are the secondary metabolites in plants and are considered reducing agents with capabilities of protecting humans from inflammation and oxidative stress. Acute exercise works as a stressor during and after performance, with the capability of causing inflammation and oxidative stress. The purpose of this research is to determine the effect of polyphenol supplementation on inflammatory markers (C-Reactive Protein, CRP; High-Sensitivity C-Reactive Protein, HS-CRP; Interleukin-6, IL-6; Interleukin-8, IL-8; and Tumor Necrosis Factor Alpha, TNF-α) and oxidative stress marker (Malondialdehyde, MDA) after acute exercise. It is hypothesized that acute exercise induced inflammation and oxidative stress will be decreased by polyphenols supplementation. A systematic review with meta-analysis was used to extract pertinent data identifying the changes of inflammatory and oxidative stress markers post-acute exercise, and polyphenol supplementation. PubMed was searched using key words "polyphenol inflammation exercise" and "polyphenol oxidative stress exercise", which produced 243 records for screening ("polyphenol inflammation exercise", results produced: n = 98, and "polyphenol oxidative stress exercise", results produced: n = 145). After screening all records and removing all duplicates, each article was assessed for eligibility based on exclusion and inclusion criteria. The total number of articles identified to be included in the study for quantitative synthesis totaled 14 ("polyphenol inflammation exercise", n = 10, and "polyphenol oxidative stress exercise", n = 4). These interventional studies focused on quantitative data pertaining to the

effects of supplementation of polyphenols on inflammatory and oxidative stress markers after acute exercise, including single-, double-, and triple-blinded designs; and randomized, placebo-controlled, and crossover designs. Data were collected using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All data collected was extracted and entered in R for statistical data analysis to create a forest plot depicting a graphical display of the results collected. A standard mean difference (SMD) comparing supplementation to placebo groups was established for all markers data extracted from this study. The results regarding the effects of polyphenol supplementation on post-acute exercise induced inflammation and oxidative stress markers varied across all studies evaluated. Based on the statistical analysis for the SMD between supplementation and control groups of each study, we found: (1) CRP, IL-8 and TNF-α levels were not affected by polyphenols supplementation after acute exercise; (2) IL-6 and MDA levels were significantly lowered with polyphenols supplementation after acute exercise. Thus, we concluded polyphenols supplementation could reduce inflammatory marker IL-6 and oxidative stress marker MDA induced by acute exercise.

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CHAPTER ONE: AN INTRODUCTION TO POLYPHENOLS, INFLAMMATORY AND OXIDATIVE STRESS MARKERS

1.1 Polyphenols

Polyphenols are the secondary metabolites in plants and largely provide their defense against ultraviolet radiation or aggression by pathogens. They are considered reducing agents and may lead to protecting humans from inflammation and oxidative stress. The benefits of human consumption can be examined and explored through gaining insight into the functions and sources of plant polyphenols. There are approximately 8,000 different polyphenols consisting of flavonoids, stilbenes, lignans, and phenolic acids (Tweed, 2018).

Flavonoids are a type of plant polyphenols, further categorized as flavonols, flavones, flavanones, flavanols, isoflavones and anthocyanins. Flavonols protect plants from the damage of ultraviolet rays. Additionally, flavonols protect people against poor circulation and elevated cholesterol. The skins of fruits and vegetables are the top sources of flavonols. Flavones act to relax blood vessels. Yellow and green fruits and vegetables are the predominant sources of flavones. Flavanones work with Vitamin C, are anti-inflammatory, and beneficial to heart health. Flavones are found in citrus fruits, such as oranges and lemons. Flavanols also known as catechins, are believed to protect against dementia. Sources of flavanols include plums, prunes, berries, and black tea. Quercetin, found in asparagus, is a type of flavanol available in supplements for hay fever, hives, asthma, and eczema. Isoflavones help balance hormones, particularly for females in the early stages leading up to menopause. The major sources of isoflavones are soy-based foods and supplements made from soy or red clover. Anthocyanins are

found in red, blue, and purple plants; and may assist in lowering the risk of heart disease, stroke, and cancer.

Stilbenes are naturally occurring phenolic compounds found in plants. As a polyphenol, stilbenes are in small quantities in food. Resveratrol is a well-known stilbene found in grape skins, red wine, and peanuts.

Lignans are phenolic compounds often found frequently in fiber-rich plants. As a polyphenol, lignans can be found in seeds, grains, fruits, and vegetables. Flaxseed is the richest source of lignans followed by sesame seeds. Lignans balance hormones and lower chronic inflammation, blood pressure, and elevated cholesterol.

Phenolic acids are types of aromatic acid compounds distributed among various parts of plants including roots, leaves, fruits and vegetables. Sources of phenolic acids are predominantly onions, radishes, olives and olive oil, berries, cocoa, flaxseed, chestnut, sage, and rosemary. Phenolic acids protect against coronary artery disease, stroke, and cancers.

Supplementation can be utilized to obtain the health benefits of consuming polyphenol rich fruits and vegetables. This supplementation can be accomplished with polyphenol rich multi-vitamins, fruit and vegetable powders, and standalone supplements. Some examples of polyphenol supplementation are the consumption of curcumin, grape seed extract, green tea extract, pterostilbene, pycnogenol, quercetin, and resveratrol.

The anti-inflammatory and anti-oxidative properties of plant polyphenols suggest there may be benefit for human consumption. This study will focus on collecting and analyzing data from various studies centered on polyphenol supplementation and the impact that supplementation has on inflammatory and oxidative stress markers post-acute exercise.

1.2 Inflammatory Markers

Inflammation is described by a surge of cellular and molecular events resulting in an increase in body temperature, capillary dilatation, and production of blood-borne soluble components. The responses can be induced by stressors and are essential for natural tissue homeostasis; and to initiate the elimination of noxious compounds and damaged tissue. Quantifiable immune parameters impacted by exercise include changes in peripheral blood cell numbers, granulocyte activity, natural killer cell cytotoxic activity, lymphocyte proliferation, and cytokine levels in plasma, among others (Cerqueira, Marinho, Neiva, & Lourenço, 2020). Inflammatory markers are frequently used in medical care for diagnosis and monitoring of inflammatory conditions, infections, autoimmune conditions, and cancers (Watson et al., 2019). Chronic inflammation has a significant part in accelerating the aging process and is closely associated with the initiation and progression of a wide range of age-related diseases. Physical exercise is viewed as beneficial in alleviating the conditions associated with chronic inflammation (Zheng et al., 2019). Current interest to the inflammatory process in medical care has increased interest in the inflammatory response to exercise.

Exercise works as a stressor during and after performance, with the capability of causing inflammation. Acute exercise stimulates an increase in plasma pro-inflammatory and anti-inflammatory cytokines. Research has indicated the pro-inflammatory and anti-inflammatory balance during and immediately post exercise is contingent on several factors, which include the health status of the individual, intensity or duration of exercise, glucose availability, and sampling time (Flynn, McFarlin, & Markofski, 2007). In addition, it has also been suggested familiarity of the exercise, as well as the age the participants can contribute to the inflammatory response from exercise (Cerqueira et al., 2020). The response of inflammatory markers to muscle

contraction and exercise activity indicates increased levels of inflammatory markers can be observed in the bloodstream acutely after exercise. This may be attributed to intense exercise or a substantial mechanical load on the muscle tissue (King, Carek, Mainous, & Pearson, 2003).

This systematic review focused on evaluating the levels of inflammatory makers CRP, HS-CRP, IL-6, IL-8, and TNF-α after acute exercise and an intervention involving polyphenol supplementation. There were 10 studies included for systematic review regarding evaluating levels of inflammatory markers after polyphenol supplementation and acute exercise. Some of the studies focused on multiple inflammatory markers. Each study focused on different polyphenol supplementation and acute exercise protocol. Of the 10 studies included in this research, 4 evaluated CRP, 3 evaluated HS-CRP, 5 evaluated IL-6, 6 evaluated IL-8, and 3 evaluated TNF-α.

1.2.1 C-Reactive Protein & HS-CRP (Acute Exercise & Intervention)

CRP is considered an acute phase protein and is an early sign of infectious or inflammatory conditions (Clyne & Olshaker, 1999). It is produced in the liver. Levels of CRP have been associated with frailty, morbidity, and mortality. There are lower levels of CRP in people who conduct moderate exercise compared to inactive people (Cerqueira et al., 2020). As an acute phase protein, CRP binds to the surfaces of apoptotic cells, which results in amplification of the classical complement pathway activation, reduced terminal complement component assembly, increased phagocytosis by macrophages, and sustained production of TGF-β. The classical pathway of complement and CRP seem to work together for the clearance of apoptotic cells in an anti-inflammatory manner. The key function of CRP promotes the clearance of dying cells (Gershov, Kim, Brot, & Elkon, 2000).

Exercise can lower CRP levels with and without weight loss. The CRP levels can be lowered using exercise for clinical and healthy populations. A previously completed systematic review with meta-analysis established the duration, frequency, and mode of exercise were not significantly correlated to the change in CRP levels. In the same study, the following three impacts were noted: (1) Exercise should be incorporated into a lifestyle intervention aimed at lowering CRP levels. (2) Larger decrease in CRP protein is detected because of exercise when complemented by a decrease in body weight or adiposity. (3) Encouraging people to be physically active can lead to beneficial changes in CRP level (Fedewa, Hathaway, & Ward-Ritacco, 2017).

For the purposes of this study, the markers for CRP and HS-CRP were combined for analysis. Both are the same protein and inflammatory marker; however, HS-CRP is a more sensitive test compared to the standard test for CRP. The sensitivity of the test allows for identification of smaller trace amounts of the marker the standard CRP test would not likely detect.

The four evaluated studies for this systematic review focusing on CRP levels utilized a variety of different acute exercise protocols and supplementation to assess the effectiveness of polyphenol supplementation and the impact the supplementation has on CRP levels post-acute exercise. The acute exercise protocols and supplementation used were as follows: an adapted version of the Loughborough Intermittent Shuttle Test (LIST) (tart cherry juice), cycling (freeze-dried fruit and vegetable juice powder), running (polyphenol enriched protein powder), and eccentric elbow flexion repetitions (pomegranate extract).

Efforts have been made to investigate the effects of supplementation with tart cherry juice on markers of recovery after intermittent exercise under habitual dietary conditions.

Participants completed acute exercise experimental protocol to evaluate CRP levels after supplementation and exercise. They conducted an adapted version of LIST, which consisted of a countermovement jump, 20-m sprint, and maximal voluntary isometric contraction. The adapted LIST consisted of 6 × 15-minute sections from LIST followed by 12 × 20-m maximal sprints with a 10-m deceleration zone, which departed every 60 seconds. The adaptations were to account for the stop, start, and change of direction nature of team sports, specifically the demands of football. The acute exercises in the adapted LIST is exercise protocol the researcher established induced muscle damage and caused inflammation, thus impacting levels of CRP markers. To evaluate CRP levels and determine the effectiveness of polyphenol supplementation after performing the adaptation of LIST, the researcher supplemented participants with either a placebo (n = 10) or tart cherry juice (n = 10). Supplementation of 30 ml of tart cherry juice occurred twice daily for eight consecutive days (five days pre, day of, and two days post LIST). The results indicated there was no significant differences throughout recovery between supplementation with tart cherry juice versus placebo for CRP. The researcher noted the study failed to observe a significant difference for CRP based on the belief the adaptations for LIST were not severe enough to cause an elevated inflammatory response. Additionally, CRP was the only inflammatory marker assessed; therefore, the researcher suggests future research evaluate multiple inflammatory markers to better assess the inflammatory response. The marker data evaluated 24 hours post exercise was as follows: PLA 2.071 +/- 2.03 mg/L and SUP 0.831 +/- 1.145 mg/L (Quinlan & Hill, 2019).

A freeze-dried fruit and vegetable juice powder was investigated as a countermeasure nutritional strategy to exercise-induced inflammation, oxidative stress, and immune perturbations in trained cyclists. Cycling was utilized as exercise protocol. During a 3-day period of endurance

cycling bouts, subjects cycled at 70%–75% VO2max for 2.25 hour per day, followed by a 15-min time trial. Participants cycled with their own bicycles on CompuTrainers. To evaluate CRP levels and determine the effectiveness of polyphenol supplementation after cycling, the researcher supplemented participants with either a placebo (n = 17) or freeze-dried fruit and vegetable juice powder (n = 16). Supplementation consisted of 230 mg/day for 17 days, which included the 3-day exercise period (days 15-17). The results indicated there were no significant interaction effects found and supplementation for 17 days did not change exercise-induced alterations in inflammation. The marker data evaluated immediately post exercise was as follows: PLA 2.12 +/- 2.05 mg/L and SUP 2.48 +/- 2.07 mg/L (Knab et al., 2014).

Polyphenol supplementation was utilized in a study as a countermeasure to exercise-induced inflammation and oxidative stress. Participants completed a 3-day period of intensified acute exercise by running on treadmills for 2.5 hours at approximately 70% VO2max to induce transient immune dysfunction, inflammation, oxidative stress, muscle damage, and muscle soreness. To evaluate CRP levels and determine the effectiveness of polyphenol supplementation after running, the researcher supplemented participants with either a placebo (n = 15) or polyphenol enriched protein powder (n = 16). Supplementation consisted of 20 g twice per day (40 g total) of polyphenol enriched powder over a 17-day period prior to exercise protocol. The researcher indicated participants exhibited significant inflammation, oxidative stress, and muscle soreness after running at high intensity for 7.5 hours during the 3-day running period; however, no differences in CRP marker levels was noted. The marker data evaluated 14 hours after the third bout of exercise protocol was as follows: PLA 4.53 +/- 2.86 mg/dL; SUP 3.39 +/- 2.54 mg/dL (Nieman et al., 2013).

During a study attempting to determine if supplementation with pomegranate extract improved recovery of skeletal muscle strength after eccentric exercise, participants utilized a Biodex isokinetic dynamometer to cause acute muscle damage from the exercise and facilitate the inflammatory process. Participants performed two sets of 20 maximal eccentric elbow flexion repetitions. After completing the first set, subjects rested four min before performing the second set. To evaluate CRP levels and determine the effectiveness of polyphenol supplementation after performing eccentric elbow flexion repetitions, the researcher supplemented participants with either a placebo (n = 16) or pomegranate extract (n = 16). Supplementation consisted of 500 ml of pomegranate extract for 9 days prior to exercise protocol. The researcher noted there was no significant changes in CRP marker levels between PLA or SUP treatments. Furthermore, it was noted the study was unable to detect a postexercise increase from baseline in either treatment. The researcher speculated the results could either be due to the amount of muscle mass experiencing damage was too small; CRP markers were not reflective of inflammation under the experimental conditions; or perhaps inflammation did not occur. The marker data evaluated 24 hours post exercise was as follows: PLA 1.66 +/- 1.87 ng/mL; SUP 1.97 +/- 0.97 ng/mL (Trombold, Barnes, Critchley, & Coyle, 2010).

The three evaluated studies for this systematic review focusing on HS-CRP levels utilized a variety of different acute exercise protocols and supplementation to assess the effectiveness of polyphenol supplementation and the impact the supplementation has on HS-CRP levels post-acute exercise. The acute exercise protocols and supplementation used were as follows: 3200 m run to exhaustion (grape juice), single leg knee extensions (cacao juice), and adapted version of LIST (montmorency tart cherry).

To evaluate the effects of a single dose of grape juice on physical performance, oxidative stress, inflammation and muscle damage, research was conducted; wherein, participants conducted two separate running tests at $VO2_{max}$ until exhaustion on a treadmill. The test was conducted a week apart. To evaluate HS-CRP levels and determine the effectiveness of polyphenol supplementation after performing a 3200 m run to exhaustion, the researcher supplemented participants with either a placebo (n = 7) or grape juice (n = 7). Supplementation consisted of 10 ml/kg of PLA or grape juice 2 hours prior to the exercise protocol to increase bioavailability of the polyphenolic compounds present in the grape juice drink. The results demonstrated an improvement in physical performance assessed during the study; however, HS-CRP did not change when comparing PLA to SUP participants. The marker data evaluated immediately after exercise was as follows: PLA 1.5 +/- 1.6 mg/dl and SUP 1.5 +/- 1.2 mg/dl (de Lima Tavares Toscano et al., 2019).

Efforts were made to study whether consumption of cacao juice enhanced recovery of muscle function following intensive knee extension exercise. As exercise protocol, participants completed two trials of 10 sets of 10 single leg knee extensions at ~80% one repetition maximum. To evaluate HS-CRP levels and determine the effectiveness of polyphenol supplementation after performing single leg knee extensions, the researcher supplemented participants with either a placebo (n = 10) or cacao juice (n = 10). Supplementation of 330 ml of PLA or cacoa juice occurred once daily for 10 days. It should be noted, the exercise protocol occurred on day eight of supplementation. The results indicated the supplementation prior to exercise protocol had no significant effect on inflammation (HS-CRP). The marker data evaluated 24 hours post exercise was as follows: PLA 0.66 +/- 0.68 mg/L and SUP 0.73 +/- 0.61 mg/L (Morgan, Wollman, Jackman, & Bowtell, 2018).

The supplementation of Montmorency tart cherry concentrate was studied to determine if supplementation influenced markers of recovery following prolonged, intermittent sprint activity. Participants completed an adapted version of LIST consisting of counter movement jump, 20 m sprint time (20 m), and maximal voluntary isometric contraction of the knee extensors. To evaluate HS-CRP levels and determine the effectiveness of polyphenol supplementation after performing an adapted version of LIST, the researcher supplemented participants with either a placebo (n = 8) or Montmorency tart cherry (n = 8). Supplementation of 30 ml of Montmorency tart cherry occurred twice daily for 8 consecutive days. It should be noted, exercise protocol occurred on day five of supplementation. The results indicated the supplementation prior to exercise protocol had no significant effect on levels of HS-CRP. The marker data evaluated 24 hours post exercise was as follows: PLA 2.93 +/- 2.73 pg/mL and SUP 1.94 +/- 0.88 pg/mL (Bell, Stevenson, Davison, & Howatson, 2016).

1.2.2 Interleukin-6 (Acute Exercise & Intervention)

Skeletal muscle fibers express IL-6, which is regulated by muscle contractions, at both the messenger ribonucleic acid (mRNA) and the protein levels. IL-6 increases insulin-stimulated glucose disposal and fatty acid oxidation in humans. It is released from working skeletal muscle and contributes to the systemic circulation (Nielsen & Pedersen, 2007). The net release of IL-6 from skeletal muscle account for increase in arterial concentration resulting from exercise. Higher amounts of IL-6 are generated in response to exercise more than any other cytokine. IL-6 is known to induce hepatic glucose output and to induce lipolysis. This indicates IL-6 possibly represents an important connection between contracting skeletal muscles and exercise-related metabolic changes (Pedersen, Steensberg, & Schjerling, 2001).

Active skeletal muscles are the major source of IL-6 production during exercise and their production and clearance is extremely high during exercise (Gleeson, 2000). IL-6 noticeably increases after endurance exercise lasting longer than several hours, for example, marathons and triathlons. The response of IL-6 is not as substantial during and after short-duration intensive exercise and eccentric-contraction exercise. The responses are related to exercise intensity and not dependent on exercise-induced muscle damage (physiological load/stress). IL-6 can be considered good for athletes for optimizing energy substrate utilization for endurance performance; however, it may compromise their immune status by inducing systemic inflammation and increasing susceptibility to infections (Suzuki, 2018).

The five evaluated studies for this systematic review focusing on IL-6 levels utilized a variety of different acute exercise protocols and supplementation to assess the effectiveness of polyphenol supplementation and the impact the supplementation has on IL-6 levels post-acute exercise. The acute exercise protocols and supplementation used were as follows: single leg knee extensions (cacao juice), 75 km cycling (bananas or pears), 15-minute cycling time trials (freeze-dried fruit and vegetable juice powder), running (polyphenol enriched protein powder), and eccentric elbow flexion repetitions (pomegranate extract).

Consumption of cacao juice was studied to determine if it enhances the recovery of muscle function following intensive knee extension exercise. As exercise protocol, participants completed two trials of 10 sets of 10 single leg knee extensions at ~80% one repetition maximum. To evaluate IL-6 levels and determine the effectiveness of polyphenol supplementation after performing single leg knee extensions, the researcher supplemented participants with either a placebo (n = 10) or cacao juice (n = 10). Supplementation of 330 ml of PLA or cacoa juice occurred once daily for 10 days. It should be noted, the exercise protocol

occurred on day eight of supplementation. The results of the study indicated the supplementation prior to exercise protocol had no significant effect on inflammation (IL-6). The marker data evaluated 24 hours post exercise was as follows: PLA 1.15 +/- 1.07 pg/mL; SUP 1.44 +/- 1.34 pg/mL (Morgan et al., 2018).

In a study focused on evaluating the influence bananas and pears had on exercise performance and recovery, participants completed three 75-km cycling time trials separated by two weeks between each trial. To evaluate IL-6 levels and determine the effectiveness of polyphenol supplementation, the researcher supplemented participants with either a placebo (n = 20) or bananas (a) (n = 20) or pears (b) (n = 20). Supplementation of either 5 mL/kg water only, or 0.4 g/kg carbohydrate from ripe cavendish bananas or bosc pears occurred 20 minutes prior to each 75-km cycling trial. Every participant consumed 3 mL/kg water every 15 min. In addition to water, the participants randomized to the banana and pear trials also ingested 0.15 g/kg carbohydrate every 15 min. There were no other beverages or food consumed during the cycling time trials and 1.5-h recovery. The results indicated there were insignificant reaction effects for either supplement when evaluating IL-6 marker levels. The marker data evaluated 1.5 hours post exercise was as follows: PLA 3.02 +/- 0.44 pg/mL, SUP a 2.53 +/- 0.39 pg/mL, and SUP b 2.37 +/- 0.22 pg/mL (Nieman et al., 2015).

A freeze-dried fruit and vegetable juice powder was investigated as a countermeasure nutritional strategy to exercise-induced inflammation, oxidative stress, and immune perturbations in trained cyclists. Cycling was utilized as exercise protocol. During a 3-day period of endurance cycling bouts, subjects cycled at 70%–75% VO2max for 2.25 hour per day, followed by a 15-min time trial. Participants cycled with their own bicycles on CompuTrainers. To evaluate IL-6 levels and determine the effectiveness of polyphenol supplementation after cycling, the

researcher supplemented participants with either a placebo (n = 17) or freeze-dried fruit and vegetable juice powder (n = 16). Supplementation consisted of 230 mg/day for 17 days, which included the 3-day exercise period (days 15-17). The results indicated there were no significant interaction effects found and supplementation for 17 days did not change exercise-induced alterations in inflammation. The marker data evaluated immediately post exercise was as follows: PLA 0.66 +/- 0.36 pg/mL; SUP 0.69 +/- 0.32 pg/mL (Knab et al., 2014).

Polyphenol supplementation was utilized in a study as a countermeasure to exercise-induced inflammation and oxidative stress. Participants completed a 3-day period of intensified acute exercise by running on treadmills for 2.5 hours at approximately 70% VO2max to induce transient immune dysfunction, inflammation, oxidative stress, muscle damage, and muscle soreness. To evaluate IL-6 levels and determine the effectiveness of polyphenol supplementation after running, the researcher supplemented participants with either a placebo (n = 15) or polyphenol enriched protein powder (n = 16). Supplementation consisted of 20 g twice per day (40 g total) of polyphenol enriched powder over a 17-day period prior to exercise protocol. The researcher indicated participants exhibited significant inflammation, oxidative stress, and muscle soreness after running at high intensity for 7.5 hours during the 3-day running period; however, no differences in IL-6 were noted. The marker data evaluated 14 hours after the third bout of exercise protocol was as follows: PLA 0.95 +/- 1.66 pg/mL; SUP 0.530 +/- 0.43 pg/mL (Nieman et al., 2013).

During a study attempting to determine if supplementation with pomegranate extract improved recovery of skeletal muscle strength after eccentric exercise, participants utilized a Biodex isokinetic dynamometer to cause acute muscle damage from the exercise and facilitate the inflammatory process. Participants performed two sets of 20 maximal eccentric elbow

flexion repetitions. After completing the first set, subjects rested 4 min before performing the second set. To evaluate IL-6 levels and determine the effectiveness of polyphenol supplementation after performing eccentric elbow flexion repetitions, the researcher supplemented participants with either a placebo (n = 16) or pomegranate extract (n = 16). Supplementation consisted of 500 ml of pomegranate extract for 9 days prior to exercise protocol. The researcher noted there was no significant changes in IL6 marker levels between PLA or SUP treatments. Furthermore, it was noted the study was unable to detect a postexercise increase from baseline in either treatment. The researcher speculated the results could either be due to the amount of muscle mass experiencing damage was too small; IL-6 markers were not reflective of inflammation under the experimental conditions; or perhaps inflammation did not occur. The marker data evaluated 24 hours post exercise was as follows: PLA 2.12 +/- 2.99 pg/mL; SUP 1.39 +/- 0.97 pg/mL (Trombold et al., 2010).

1.2.3 Interleukin-8 (Acute Exercise & Intervention)

Much like IL-6, skeletal muscle fibers express IL-8, which is regulated by muscle contractions, at both the mRNA and the protein levels. Both IL-6 and IL-8 are released from working skeletal muscle; however, because IL-6 contributes to the systemic circulation, there are only a small net release of IL-8 found. This suggests IL-8 may exert its effects locally in the muscle (Nielsen & Pedersen, 2007).

IL-8 is released into the circulation because of prolonged, intense exercise conditions; however, short-time intensive exercise also enhances concentration of plasma IL-8. These findings suggest duration and intensity of exercise might be important for the release of IL-8. IL-8 noticeably increases after endurance exercise lasting longer than several hours, for example, marathons and triathlons. The response of IL-8 is not as substantial during and after short-

duration intensive exercise and eccentric-contraction exercise. The responses are related to exercise intensity and not dependent on exercise-induced muscle damage (physiological load/stress) (Suzuki, 2018).

The six evaluated studies for this systematic review focusing on IL-8 levels utilized a variety of different acute exercise protocols and supplementation to assess the effectiveness of polyphenol supplementation and the impact the supplementation has on IL-8 levels post-acute exercise. The acute exercise protocols and supplementation used were as follows: 75-km cycling time trials (yellow banana or cavendish banana), resistance exercise session (squat, leg press, and leg extensions) (proprietary polyphenol blend of water-extracted green and black tea (camellia sinensis)), adapted version of LIST (Montmorency tart cherry), 75-km cycling trials (cavendish bananas or pears), 15-minute cycling time trial (freeze-dried fruit and vegetable juice powder), and running (polyphenol enriched protein powder).

To evaluate the impacts consumption of Cavendish bananas or mini-yellow bananas had on exercise-induced IL-8 marker levels, a study was developed; wherein, participants completed four 75-km cycling time trials using personally owned bicycles on CompuTrainer Pro Model 8001 trainers. To evaluate IL-8 levels and determine the effectiveness of polyphenol supplementation after performing 75-km cycling time trials, the researcher supplemented participants with either a placebo (n = 20) or yellow banana (a) (n = 20) or cavendish banana (b) (n = 20). Supplementation of 0.4 g/kg carbohydrate from cavendish bananas or mini-yellow bananas occurred in an overnight fasted state 20 minutes prior to exercise protocol. The results indicated there was a significant difference in the reduction of IL-8 with both supplementation interventions when compared to placebo. The marker data evaluated 21 hours post exercise was

as follows: PLA 4.75 +/- 0.5 pg/mL, SUP a 5.01 +/- 0.5 pg/mL, and SUP b 4.51 +/- 0.4 pg/mL (Nieman, Gillitt, Sha, Esposito, & Ramamoorthy, 2018).

Research was conducted to examine the effect of resistance exercise on the production, recruitment, percentage, and adhesion characteristics of granulocytes with and without polyphenol supplementation. In the study, participants completed a resistance exercise session consisting of six sets of 10 repetitions of squats and four sets of 10 repetitions of leg press and leg extension exercises. Each exercise was completed at 70% of the participant's previously determined 1-RM with 90 sec of rest between each set. To evaluate IL-8 levels and determine the effectiveness of polyphenol supplementation after performing resistance exercise session (squat, leg press, and leg extensions), the researcher supplemented participants with either a placebo (n = 15) or proprietary polyphenol blend of water-extracted green and black tea (camellia sinensis) (n = 13). Supplementation of 1 g of proprietary polyphenol blend of water-extracted green and black tea (camellia sinensis) while supervised and 2,000 mg unsupervised occurred daily for 28 days. The results indicated there was no significant decrease in IL-8 marker levels when comparing supplementation to placebo. The marker data evaluated 24 hours post exercise was as follows: PLA 54.3 +/- 43.7 pg/mL and SUP 44.3 +/- 50.9 pg/mL (Jajtner et al., 2016).

The supplementation of Montmorency tart cherry concentrate was studied to determine if supplementation influenced markers of recovery following prolonged, intermittent sprint activity. Participants completed an adapted version of LIST consisting of counter movement jump, 20 m sprint time (20 m), and maximal voluntary isometric contraction of the knee extensors. To evaluate IL-8 levels and determine the effectiveness of polyphenol supplementation after performing an adapted version of LIST, the researcher supplemented participants with either a placebo (n = 8) or Montmorency tart cherry (n = 8). Supplementation of

30 ml of Montmorency tart cherry occurred twice daily for 8 consecutive days. It should be noted, exercise protocol occurred on day five of supplementation. The results indicated the supplementation prior to exercise protocol had no significant effect on levels of IL-8. The marker data evaluated 24 hours post exercise was as follows: PLA 2.5 +/- 0.76 pg/mL; SUP 2.23 +/- 0.53 pg/mL (Bell et al., 2016).

In a study focused on evaluating the influence bananas and pears had on exercise performance and recovery, participants completed three 75-km cycling time trials separated by two weeks between each trial. To evaluate IL-8 levels and determine the effectiveness of polyphenol supplementation, the researcher supplemented participants with either a placebo (n = 20) or bananas (a) (n = 20) or pears (b) (n = 20). Supplementation of either 5 mL/kg water only, or 0.4 g/kg carbohydrate from ripe cavendish bananas or bosc pears occurred 20 minutes prior to each 75-km cycling trial. Every participant consumed 3 mL/kg water every 15 min. In addition to water, the participants randomized to the banana and pear trials also ingested 0.15 g/kg carbohydrate every 15 min. There were no other beverages or food consumed during the cycling time trials and 1.5-h recovery. The results indicated there were insignificant reaction effects for either supplement when evaluating IL-8 marker levels. The marker data evaluated 1.5 hours post exercise was as follows: PLA 7.77 +/- 0.88 pg/mL, SUP a 7.44 +/- 0.59 pg/mL and SUP b 7.61 +/- 0.58 pg/mL (Nieman et al., 2015).

A freeze-dried fruit and vegetable juice powder was investigated as a countermeasure nutritional strategy to exercise-induced inflammation, oxidative stress, and immune perturbations in trained cyclists. Cycling was utilized as exercise protocol. During a 3-day period of endurance cycling bouts, subjects cycled at 70%–75% VO2max for 2.25 hour per day, followed by a 15-min time trial. Participants cycled with their own bicycles on CompuTrainers. To evaluate IL-8

levels and determine the effectiveness of polyphenol supplementation after cycling, the researcher supplemented participants with either a placebo (n = 17) or freeze-dried fruit and vegetable juice powder (n = 16). Supplementation consisted of 230 mg/day for 17 days, which included the 3-day exercise period (days 15-17). The results indicated there were no significant interaction effects found and supplementation for 17 days did not change exercise-induced alterations in inflammation. The marker data evaluated immediately post exercise was as follows: PLA 2.01 +/- 0.85 pg/mL and SUP 2.30 +/- 0.93 pg/mL (Knab et al., 2014).

Polyphenol supplementation was utilized in a study as a countermeasure to exercise-induced inflammation and oxidative stress. Participants completed a 3-day period of intensified acute exercise by running on treadmills for 2.5 hours at approximately 70% VO2max to induce transient immune dysfunction, inflammation, oxidative stress, muscle damage, and muscle soreness. To evaluate IL-8 levels and determine the effectiveness of polyphenol supplementation after running, the researcher supplemented participants with either a placebo (n = 15) or polyphenol enriched protein powder (n = 16). Supplementation consisted of 20 g twice per day (40 g total) of polyphenol enriched powder over a 17-day period prior to exercise protocol. The researcher indicated participants exhibited significant inflammation, oxidative stress, and muscle soreness after running at high intensity for 7.5 hours during the 3-day running period; however, no differences in IL-8 were noted. The marker data evaluated 14 hours after the third bout of exercise protocol was as follows: PLA 1.81 +/- 0.96 pg/mL and SUP 1.72 +/- 0.59 pg/mL (Nieman et al., 2013).

1.2.4 Tumor Necrosis Factor Alpha (Acute Exercise & Intervention)

TNF-α is a multifunctional cytokine involved in regulating inflammation and tissue injury. It is predominantly known for its pro-inflammatory role in tissue degradation. TNF-α can

be synthesized by a variety of immune and nervous cells and is rapidly released into the bloodstream by circulating monocytes and in skeletal muscle by invading macrophages after post exercise muscle damage. Additionally, it can induce necrosis and apoptosis of myocytes through intracellular signaling pathways, which is associated with a decline in muscle contractile properties and diminished performance (Townsend et al., 2015).

Exercise training significantly reduces the local muscle expression of TNF-α (Smart, Larsen, Le Maitre, & Ferraz, 2011). In the Journal of Exercise Rehabilitation 2017, documentation of a 4-week exercise training program focused on moderate intensity walking exercise on a treadmill for 60 min at 70% of maximal heart rate resulted in a significant reduction of TNF-α (Koh & Park, 2017). This study added validity in support of exercise training reducing muscle expression of TNF-α.

The three evaluated studies for this systematic review focusing on TNF-α levels utilized a variety of different acute exercise protocols and supplementation to assess the effectiveness of polyphenol supplementation and the impact the supplementation has on TNF-α levels post-acute exercise. The acute exercise protocols and supplementation used were as follows: an adapted version of LIST (Montmorency tart cherry), 75-km cycling time trials (bananas or pears), and 15-minute cycling time trials (freeze-dried fruit and vegetable juice powder).

The supplementation of Montmorency tart cherry concentrate was studied to determine if supplementation influenced markers of recovery following prolonged, intermittent sprint activity. Participants completed an adapted version of LIST consisting of counter movement jump, 20 m sprint time (20 m), and maximal voluntary isometric contraction of the knee extensors. To evaluate TNF-α levels and determine the effectiveness of polyphenol supplementation after performing an adapted version of LIST, the researcher supplemented

participants with either a placebo (n = 8) or Montmorency tart cherry (n = 8). Supplementation of 30 ml of Montmorency tart cherry occurred twice daily for 8 consecutive days. It should be noted, exercise protocol occurred on day five of supplementation. The results indicated the supplementation prior to exercise protocol had no significant effect on levels of TNF-α. The marker data evaluated 24 hours post exercise was as follows: PLA 1.83 +/- 0.90 pg/mL and SUP 1.36 +/- 0.39 pg/mL (Bell et al., 2016).

In a study focused on evaluating the influence bananas and pears had on exercise performance and recovery, participants completed three 75-km cycling time trials separated by two weeks between each trial. To evaluate TNF-α levels and determine the effectiveness of polyphenol supplementation, the researcher supplemented participants with either a placebo (n = 20) or bananas (a) (n = 20) or pears (b) (n = 20). Supplementation of either 5 mL/kg water only, or 0.4 g/kg carbohydrate from ripe cavendish bananas or bosc pears occurred 20 minutes prior to each 75-km cycling trial. Every participant consumed 3 mL/kg water every 15 min. In addition to water, the participants randomized to the banana and pear trials also ingested 0.15 g/kg carbohydrate every 15 min. There were no other beverages or food consumed during the cycling time trials and 1.5-h recovery. The results indicated there were insignificant reaction effects for either supplement when evaluating TNF-α marker levels. The marker data evaluated 1.5 hours post exercise was as follows: PLA 2.39 +/- 0.15 pg/mL, SUP a 2.42 +/- 0.12 pg/mL, and SUP b 2.43 +/- 0.14 pg/mL (Nieman et al., 2015).

A freeze-dried fruit and vegetable juice powder was investigated as a countermeasure nutritional strategy to exercise-induced inflammation, oxidative stress, and immune perturbations in trained cyclists. Cycling was utilized as exercise protocol. During a 3-day period of endurance cycling bouts, subjects cycled at 70%–75% VO2max for 2.25 hour per day, followed by a 15-

min time trial. Participants cycled with their own bicycles on CompuTrainers. To evaluate TNF-α levels and determine the effectiveness of polyphenol supplementation after cycling, the researcher supplemented participants with either a placebo (n = 17) or freeze-dried fruit and vegetable juice powder (n = 16). Supplementation consisted of 230 mg/day freeze-dried fruit and vegetable juice powder for 17 days, which included the 3-day exercise period (days 15-17). The results indicated there were no significant interaction effects found and supplementation for 17 days did not change exercise-induced alterations in inflammation. The marker data evaluated immediately post exercise was as follows: PLA 3.94 +/- 1.08 pg/mL and SUP 4.30 +/- 1.22 pg/mL (Knab et al., 2014).

1.3 Oxidative Stress Markers

Free radicals are part of the natural physiological process and are created during normal cellular function. They are both helpful or harmful to the human body, as they act as both beneficial and toxic compounds. When an abundant amount of free radicals cannot steadily be processed or in case of a poor naturally occurring antioxidant availability, free radicals accumulation creates "oxidative damage", also known as "oxidative stress" (Simioni et al., 2018). Oxidative stress results from the imbalance between reactive oxygen species formation and enzymatic and non-enzymatic antioxidants. Various identified pathologic and non-pathologic conditions could speed up the creation of free radicals or undermine the antioxidant defense system. Regular physical activity and prolonged intensive exercise despite various beneficial effects on health promotion and reduction of the risk of various chronic diseases, are oxidative stress-induced causing conditions. Exercise is associated with production of oxidative stress through over production of reactive oxygen species (ROS), to include superoxide anion (O^{2-}), hydroxyl (OHHO) and peroxyl radical (RO2). Increased production of reactive nitrogen

species to include peroxynitrite, produced from nitric oxide, are also linked to exercise-induced oxidative stress (Yavari, Javadi, Mirmiran, & Bahadoran, 2015). The markers for oxidative stress are pertinent in the evaluation of the disease status and of the health-enhancing effects of antioxidants (Marrocco, Altieri, & Peluso, 2017). Interest in oxidative stress markers and anti-oxidative medical treatment processes has increased interest in the oxidative stress responses to exercise. Oxygen demand for skeletal muscle will increase during exercise. Exercise-induced muscle damage promotes infiltration of phagocytes (neutrophils and macrophages) at the site of the damaged tissue. The physiological changes from acute exercise increase free radical production, resulting in oxidative damage to biomolecules. Biochemical and molecular biological techniques have aided in observation of oxidative damage at the cellular level and have indicated free radicals play a role in physiological adaptations after exercise training. Thus, free radicals generated by exercise are considered to both be positive and negative physiologically (Kawamura & Muraoka, 2018).

This review will focus on evaluating the levels of MDA as an oxidative stress maker after acute exercise. There were four studies included for systematic review regarding evaluating levels of oxidative stress markers after acute exercise and polyphenol supplementation and/or consumption of polyphenol-rich foods. Each study focused on different polyphenol supplementation and acute exercise protocol.

1.3.1 Malondialdehyde (Acute Exercise & Intervention)

MDA is a three-carbon chain aldehyde created during decomposition of a lipid hydroperoxide (Fisher-Wellman & Bloomer, 2009). Measurement of MDA is thought to be an important characteristic of oxidative stress assessment; however, as it is often difficult to measure because MDA exist only in trace amounts even during oxidative stress (Kawamura &

Muraoka, 2018). It is one of the most popular markers in literature to characterize lipid peroxidation (Souissi et al., 2020).

Marker levels of MDA can be impacted by exercise. The level of the increase is dependent upon the type, duration, and intensity of exercise. Exercise has previously been shown to increase oxidative and inflammatory damage. After exercise, MDA is the product of autoxidation of unsaturated fatty acids. It has been suggested, mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, phospholipase A2-dependent processes and xanthine oxidase contribute to ROS production in the human body. Thus, leading to increased oxidative damage, which MDA is a marker of (Diaba-Nuhoho et al., 2018).

The four evaluated studies for this systematic review focusing on MDA levels utilized a variety of different acute exercise protocols and supplementation to assess the effectiveness of polyphenol supplementation and the impact the supplementation has on MDA levels post-acute exercise. The acute exercise protocols and supplementation used were as follows: Olympic weightlifting exercises (snatch, clean and jerk, and squat) (pomegranate juice), treadmill running (dietary almond- and olive oil based docosahexaenoic acid and vitamin E enriched beverage), eccentric contraction-based resistance training routine (lippia citriodora extract (commercially called PLX) acronym coming from ‘‘PoLyphenol eXtract’’), and cycling (green tea extract).

Pomegranate juice supplementation was studied to determine the impact it has on oxidative stress post weightlifting exercise. Participants complete two training sessions of Olympic Weightlifting exercises (snatch, clean and jerk, and squat). They completed two sets of three repetitions at 85% of 1-RM and three sets of two repetitions at 90% of 1-RM (total of five sets per exercise). One session was with placebo and the other was with supplementation. Both sessions were separated by 48 hours. To evaluate MDA levels and determine the effectiveness of

polyphenol supplementation after performing Olympic Weightlifting exercises (snatch, clean and jerk, and squat), the researcher supplemented participants with either a placebo (n = 9) or pomegranate juice (n = 9). Supplementation of 500 mL of pomegranate juice occurred 60 min before the training sessions and 250 ml of pomegranate juice three times daily during the 48 hours preceding the two training sessions. The results indicated there was a significant difference when comparing supplementation group to placebo group post-acute exercise. The marker data evaluated 48 hours post exercise was as follows: PLA 1.76 +/- 0.24 µmol/L; and SUP 1.43 +/- 0.23 µmol/L (Ammar et al., 2017).

There was a study completed to evaluate a dietary almond and olive oil-based docosahexaenoic acid and vitamin E-enriched beverage to determine the impact it would have on physical performance, plasma and erythrocyte fatty acids' and polyphenol handling, oxidative and nitrative damage, and antioxidant and mitochondrial gene expression in young and senior athletes. Participants continuously ran on the treadmill at the speed of 60% VO2max for 5 minutes, 70% VO2max for 5 minutes and 80% VO2max for 5 minutes for three consecutive bouts with two minutes of recovery between bouts. Finally, all participants ran at 90% VO2max until exhaustion. To evaluate MDA levels and determine the effectiveness of polyphenol supplementation after running on a treadmill, the researcher supplemented participants with either a placebo (n = 5 for young and n= 3 for senior) or dietary almond- and olive oil based docosahexaenoic acid and vitamin E enriched beverage (n = 5 for young and n = 5 for senior). Supplementation of one liter of dietary almond- and olive oil based docosahexaenoic acid and vitamin E enriched beverage occurred five days per week for five weeks leading to the exercise protocol. Half of the beverage was taken in the morning and the other half before their individual daily training sessions (no prescribed exercise protocol). The results indicated there was a

significant decrease in MDA levels for supplementation in the young and senior participants when compared to placebo post-acute exercise. The marker data evaluated one hour post exercise was as follows: PLA Young 3.41 +/- 2.43 µmol/L and Senior 1.79 +/- 1.10 µmol/L; and SUP Young 1.92 +/- 1.38 µmol/L and Senior 0.77 +/- 0.57 µmol/L (Capo et al., 2016).

There was an evaluation of the effects lippia citriodora extract supplementation would have on redox status of blood cells. Participants completed a Burpee test consisting of four counts beginning in a standing position. The first count implies dropping in a squat position with both hands on the floor. In count two, the legs are extended backward in one swift motion to reach the front plank position. Count 3 participants return to the squat position in one swift movement. Finally, in count four, each participant returns to the upright standing position. All participants were asked to perform the maximum number of repetitions in one minute (four counts = one repetition). To ensure muscular exhaustion and eccentric damage occurred, all participants conducted three series of the complete test with 2 min recovery between each series. To evaluate MDA levels and determine the effectiveness of polyphenol supplementation after performing an eccentric contraction-based resistance training routine, the researcher supplemented participants with either a placebo (n = 8) or lippia citriodora extract (n = 8). Supplementation of 250ml of lippia citriodora extract occurred daily for 21 days. The results indicated a significant decrease in MDA marker levels when comparing supplementation groups to placebo groups post-acute exercise. The marker data evaluated between 10-12 hours post exercise was as follows: PLA 249 +/- 29 µmol/L; and SUP 91 +/- 9 µmol/L (Carrera-Quintanar et al., 2015).

The effect of green tea extract supplementation on exercise-induced stress parameters in sprinters was conducted. Participants completed two four-week treatment periods of polyphenol

or placebo supplementation. The participants performed a repeated cycle sprint test at the end of each treatment period. The tests were conducted on a cycle ergometer and consisted of four consecutive 15-s bouts (4 X 15 s). Each bout was separated by 1-min rest intervals. Each participant was asked to cycle as fast as they could against a constant load of 75 g/kg body weight for 15 s. To evaluate MDA levels and determine the effectiveness of polyphenol supplementation after cycling, the researcher supplemented participants with either a placebo (n = 16) or green tea extract (n = 16). Supplementation of 980 mg of green tea extract occurred daily for two four-week treatment periods. The results indicated a significant decrease in MDA marker levels when comparing supplementation to placebo post-acute exercise. The marker data evaluated 24 hours post exercise was as follows: PLA 0.86 +/- 0.36 µmol/L and SUP 0.53 +/- 0.08 µmol/L (Jowko, Dlugolecka, Makaruk, & Cieslinski, 2015).

CHAPTER TWO: EFFECTS OF POLYPHENOLS SUPPLEMENTATION ON INFLAMMATION AFTER ACUTE EXERCISE: A SYSTEMATIC REVIEW WITH META-ANALYSIS

2.1 Introduction/Background

Exercise works as a stressor during and after performance, with the capability of causing inflammation. Acute exercise stimulates an increase in plasma inflammatory markers CRP, IL-6, IL-8 and TNFa. The inflammatory process during and immediately post exercise is contingent on several factors, which include the health status of the individual, intensity or duration of exercise, glucose availability, and sampling time (Flynn, McFarlin, & Markofski, 2007). Polyphenols are potent reducing agents with anti-inflammatory and antioxidants properties capable of fighting inflammation, DNA damage and lipid oxidation (Tweed, 2018). The overall impact of polyphenol supplementation on post-acute exercise inflammatory markers varies based on the type.

The 10 evaluated studies of experimental research for this systematic review spanned from 2010-2019 focusing on a variety polyphenols supplementation as an intervention for acute exercise-induced CRP, IL-6, IL-8 and TNF-α marker levels. The acute exercise protocols, supplementation and inflammatory markers assessed were as follows: 3200 m run to exhaustion, grape juice, HS-CRP (Toscano, 2019); countermovement jump, 20m sprint, maximal voluntary isometric contraction, tart cherry juice, CRP (Quinlan, 2019); single leg knee extensions, cacao juice, HS-CRP & IL-6 (Morgan, 2018); 75-km cycling time trials, yellow banana or cavendish banana, IL-8 (Nieman, 2018); squat, leg press, & leg Extensions, water-extracted green & black tea (camellia sinensis), IL-8 (Jaitner, 2016); countermovement jump, 20m sprint, and maximal voluntary isometric contraction), montmorency tart cherry, HS-CRP, IL-8 & TNF-α (Bell, 2016);

75-km cycling time trials, cavendish bananas or pears, IL-6, IL-8 & TNF-α (Nieman, 2015); 15-minute cycling trial, freeze-dried fruit & vegetable juice powder, CRP, IL-6, IL-8 & TNF-α (Nieman, 2013); running, polyphenol enriched protein powder, CRP, IL-6 & IL-8 (Knab/2014); and eccentric elbow flexion repetitions, pomegranate extract, CRP & IL-6 (Trombold/2010).

We hypothesize that acute exercise induced inflammatory markers CRP, IL-6, IL-8 and TNF-α will be decreased by polyphenols supplementation.

2.2 Methods

This meta-analysis was based on the pertinent inflammatory marker data obtained during the systematic review of published literature regarding inflammatory response post-acute exercise and the anti-inflammatory properties of polyphenol consumption. The total number of articles identified from PUBMED to be included in the study for quantitative synthesis applicable to the key terminology "polyphenol inflammation exercise" were 12 (Appendix C, Figure 1). Inflammatory marker data was collected using the PRISMA guidelines. All data collected was grouped by individual inflammatory marker; then extracted into a separate Excel.csv worksheet per group and entered in R for statistical data analysis to create a forest plot depicting a graphical display of the results collected.

2.3 Results

All studies included in this meta-analysis used a wide variety of acute exercise protocol to cause exercise-induced inflammation and supplemented with various polyphenolic substances in order to determine if there was any impact on the inflammatory markers when compared to a placebo. Additionally, each study varied in sampling timepoint from immediately post exercise – 48hours, as this time period captured appropriate peak measurements of inflammatory marker data. Data extracted from the immediately post exercise timeframe was extracted solely because

samples were not obtained by the researcher at any other time frame in the respective study. If there were multiple sampling time points, the closest sampling timepoint between 24-48 hours were extracted to capture the peak measurements of inflammatory marker data. The inflammatory marker data produced was extracted during this review to determine the SMD of the respective inflammatory marker post-acute exercise with supplementation compared to placebo. Within each study, the measurement period was consistent between the supplementation and placebo groups. Thus, this meta-analysis assesses the overall differences between supplementation and placebo as measured between immediately post exercise and 48 hours.

2.3.1 C-Reactive Protein

A total of seven studies were compared to establish the SMD of the impacts supplementation of polyphenolic compounds has on post-acute exercise CRP marker levels. The SMD for CRP was -0.12, CI between -0.42 and 0.19 mg/dl, and P = 0.60 (Appendix C, Figure 2). The data pertaining to CRP indicates supplementation has no significant impact on post-acute exercise CRP levels. The CI value indicates 95% of the time, the true population will fall between -0.42 and 0.19 mg/dl of acute exercise induced CRP levels when supplemented with polyphenolic compounds. Evidence does not support the hypothesis there would be decrease in CRP post-acute exercise as a result of polyphenol supplementation.

2.3.2 Interleukin-6

A total of five studies were compared to establish the SMD of the impacts of supplementation of polyphenolic compounds has on post exercise IL-6 levels. One of the studies evaluated two separate types of polyphenolic compounds, which brought the total number of experiments to seven to establish the SMD. The SMD for IL-6 was -0.58, CI between -0.88 and -0.29 pg/ml, and $P < 0.01$ (Appendix C, Figure 3). The data pertaining to IL-6 indicates

supplementation decreases post-acute exercise IL-6 levels. The CI value indicates 95% of the time, the true population will fall between -0.88 and -0.29 pg/ml of acute exercise induced IL-6 levels when supplemented with polyphenolic compounds. There is sufficient evidence supporting the hypothesis there would be decrease in IL-6 post-acute exercise as a result of polyphenol supplementation.

2.3.3 Interleukin-8

A total of six studies were compared to establish the SMD of the impacts of supplementation of polyphenolic compounds has on post exercise IL-8 levels. Two of the studies evaluated two separate types of polyphenolic compounds each, which brought the total number of experiments to eight to establish the SMD. The SMD for IL-8 was -0.12, CI between -0.36 and 0.13 pg/ml, and P = 0.31 (Appendix C, Figure 4). The data pertaining to IL-8 indicates supplementation did not significantly decreases post-acute exercise IL-8 levels. The CI value indicates 95% of the time, the true population will fall between -0.36 and 0.13 pg/ml of acute exercise induced IL-8 levels when supplemented with polyphenolic compounds. Evidence does not support the hypothesis there would be decrease in IL-8 post-acute exercise as a result of polyphenol supplementation.

2.3.4 Tumor Necrosis Factor Alpha

A total of three studies were compared to establish the SMD of the impacts of supplementation of polyphenolic compounds has on post exercise TNF-α levels. One of the studies evaluated two separate types of polyphenolic compounds, which brought the total number of experiments to four to establish the SMD. The SMD for TNF-α was 0.15, CI between -0.19 and 0.50 pg/ml, and P = 0.44 (Appendix C, Figure 5). The data pertaining to TNF-α indicates supplementation increased post-acute exercise TNF-α levels. The CI value indicates

95% of the time, the true population will fall between -0.19 and 0.50 pg/ml of acute exercise induced TNF-α levels when supplemented with polyphenolic compounds. Evidence does not support the hypothesis there would be decrease in TNF-α post-acute exercise as a result of polyphenol supplementation.

2.4 Discussion

The aim of the systematic review was to determine if the ani-inflammatory properties of polyphenols could attenuate post-acute exercise induced inflammation. Although the results varied across each marker, the polyphenol supplementation did in fact impact post-acute exercise induced inflammation.

There was not a notable decrease in CRP or IL-8 marker levels when comparing placebo to polyphenol supplementation. This was regardless of the polyphenolic compound used and the form of acute exercise performed. This does not mean polyphenol supplementation does not impact exercise-induced inflammation. As previously described in this thesis, CRP can be caused by a variety of medical conditions and not simply be indicative of exercise-induced inflammation. CRP is a very sensitive marker and could be affected by conditions like hormonal, exercise, and nutritional changes. In this study, HS-CRP was combined with CRP data, as this is the same protein. The sole difference is HS-CRP is a more sensitive test compared to the standard test for CRP. The sensitivity of the test allows for identification of smaller trace amounts of the marker the standard CRP test would not likely detect. Therefore, based on the overall results of CRP marker levels, it is not surprising the results of the studies testing HS-CRP did not yield any results showing a decrease in marker levels due to polyphenol supplementation. As noted during the review, it was established regarding CRP that the effect of inflammatory pathway changes on the adaptive response to exercise, require further investigation (Jackman et

al., 2018). Studies focused on evaluating IL-8 failed to show a consistent decrease in marker level post-acute exercise due to polyphenol supplementation. This is to be expected, especially given the fact IL-8 is only found in small net release locally from working muscle (Nielsen & Pedersen, 2007). IL-8 is only found in small amounts circulating in the blood stream after exercise. IL-8 is in locally contracted muscles and exerts its affects locally in the active muscle but not affecting your systemic inflammation.

The studies focusing on evaluating TNF-α showed there was an increase on the level of TNF-α post-acute exercise even with supplementation of polyphenolic compounds. Exercise training itself significantly reduces the local muscle expression of TNF-α. Upregulation of TNF-α in the plasma during exercise is likely due to being upregulated in local production in, or release from, exercised muscle tissues (Bernecker et al., 2013). TNF-α is not affected after acute exercise, especially eccentric exercise.

Of the markers evaluated, IL-6 was the only one to show a significant decrease in post-acute exercise levels when comparing placebo to polyphenol supplementation. The results for IL-6 were not all the same, as some studies reported a smaller increase in IL-6 post exercise as well as a smaller difference when comparing the placebo to the supplementation group. It is the SMD of all studies evaluated that indicate IL-6 would significantly decrease if an individual supplemented with polyphenols prior to acute exercise. Polyphenols have potent anti-inflammatory capabilities. Large amounts of IL-6 are generated and are associated with exercise-related metabolic changes, as it is a muscle derived cytokine. As noted in Chapter 1, Section 1.2.2 Interleukin-6 (Acute Exercise & Intervention), IL-6 noticeably increases after endurance exercise lasting longer than several hours, for example, marathons and triathlons. The response of IL-6 is not as substantial during and after short-duration intensive exercise and eccentric-

contraction exercise. This explains why there was a difference in the outcome of the studies focusing on IL-6, as the ones noticeably impacted by supplementation utilized exercise protocol lasting an extended period of time, such as a 75 km cycling trial.

It is clearly established throughout this review, exercise causes inflammation. Specifically, acute exercise stimulates an increase in plasma pro-inflammatory and anti-inflammatory cytokines. The pro and anti-inflammatory balance post exercise is contingent on several factors, which include the health status of the individual, intensity or duration of exercise, glucose availability, and sampling time. Referring back to (Trombold et al., 2010), where the results were directly impacted and show the relevance of exercise intensity and duration. He explained the study was unable to detect a postexercise increase from baseline in either treatment used and he suspected the results were due to the amount of muscle mass experiencing damage was too small; the inflammatory marker assessed was not reflective of inflammation under the experimental conditions; or inflammation simply did not occur.

What demonstrates polyphenol supplementation can attenuate inflammation aside from the SMD value of IL-6? Simply put, it is the established research identified in this thesis regarding the anti-inflammatory properties of plant polyphenols. It is increasingly important to understand why polyphenol supplementation impacted IL-6 in the manner it did. Polyphenols are potent antioxidants capable of fighting inflammation, DNA damage and lipid oxidation. It is understandable there would be an impact of polyphenol supplementation given their capabilities and the fact larger amounts of IL-6 are generated in response to exercise, more than any other cytokine. Additionally, IL-6 is known to induce hepatic glucose output and to induce lipolysis. IL-6 represents an important connection between contracting skeletal muscles and exercise-related metabolic changes (Pedersen et al., 2001).

Keep in mind, CRP is a very sensitive marker and could be affected by conditions like hormonal, exercise and nutritional changes; and IL-8 is only found in small amounts circulating in the blood stream after exercise. Exercise training itself significantly reduces the local muscle expression of TNF-α. Thus, leaving the IL-6 as the sole inflammatory marker assessed that is increased in abundance post exercise and impacted by the anti-inflammatory properties of polyphenols. The greatest impact supplementation had on IL-6 in this meta-analysis was with bananas (Nieman 2015a) SMD -1.16 and pears (Neiman 2015b) SMD -1.83 (Appendix C, Figure 3).

2.5 Conclusion

The evaluation of SMD data pertaining to the impacts of supplementation of polyphenolic compounds on post-acute exercise inflammatory markers varied in results. Polyphenols supplementation did not change CRP, IL-8 and TNF-α levels post-acute exercise. A significant decrease on IL-6 level was observed with supplementation of polyphenolic compounds after acute exercise. Based on the SMD from the studies evaluated, we concluded that polyphenols supplementation decreased acute exercise-induced plasma inflammatory marker IL-6.

CHAPTER 3: EFFECTS OF POLYPHENOLS SUPPLEMENTATION ON OXIDATIVE STRESS AFTER ACUTE EXERCISE: A SYSTEMATIC REVIEW WITH META-ANALYSIS

3.1 Introduction/Background

Oxidative stress results from the imbalance between reactive oxygen species formation and enzymatic and non-enzymatic antioxidants. The physiological changes from acute exercise increase free radical production, resulting in oxidative damage to biomolecules (Kawamura & Muraoka, 2018). Exercise is associated with production of oxidative stress through over production of ROS, to include superoxide anion, hydroxyl and peroxyl radical (Yavari, Javadi et al, 2015). Increased production of ROS to include peroxynitrite, produced from nitric oxide, are also linked to exercise-induced oxidative stress markers Thiobarbituric Acid Reactive Substances (TBARS) and MDA. TBARS and MDA result from the disruption in oxidant-antioxidant balance resulting from exercise and environmental extremes. Polyphenols are potent reducing agents with anti-inflammatory and antioxidants properties capable of fighting inflammation, DNA damage and lipid oxidation (Tweed, 2018). The overall impact of polyphenol supplementation on post-acute exercise oxidative stress markers varies based on the type.

The four evaluated studies of experimental research for this systematic review spanned from 2015-2017 focusing on a variety polyphenols supplementation as an intervention for acute exercise-induced MDA marker levels. The acute exercise protocols and supplementation assessed were as follows: Olympic weightlifting exercises (snatch, clean and jerk, and squat), pomegranate Juice (Ammar, 2017); treadmill running, dietary almond- and olive oil based docosahexaenoic acid and vitamin E enriched beverage (Capo, 2016); eccentric contraction-

based resistance training routine, lippia citriodora extract, (Carrera-Quintanar, 2015); and cycling, green tea extract (Jowko, 2015).

We hypothesize that acute exercise induced oxidative stress marker MDA will be decreased by polyphenols supplementation.

3.2 Methods

This meta-analysis was based on the pertinent oxidative stress marker data obtained during the systematic review of published literature regarding oxidative stress response post-acute exercise and the anti-oxidative properties of polyphenol consumption. The total number of articles identified from PUBMED to be included in the study for quantitative synthesis applicable to the key terminology "polyphenol oxidative stress exercise" were 6 (Appendix C, Figure 1). Oxidative stress marker data was collected using the PRISMA guidelines. All data collected was grouped by individual oxidative stress marker; then extracted into a separate Excel.csv worksheet per group and entered in R for statistical data analysis to create a forest plot depicting a graphical display of the results collected.

3.3 Results

All studies included in this meta-analysis used a wide variety of acute exercise protocol to cause exercise-induced oxidative stress and supplemented with various polyphenolic substances in order to determine if there was any impact on the oxidative stress markers when compared to a placebo. Additionally, each study varied in sampling timepoint from immediately post exercise – 48hours, as this time period captured appropriate peak measurements of oxidative stress marker data. Data extracted from the immediately post exercise timeframe was extracted solely because samples were not obtained by the researcher at any other time frame in the respective study. If there were multiple sampling time points, the closest sampling timepoint

between 24-48 hours were extracted to capture the peak measurements of oxidative stress marker data. The oxidative stress marker data produced was extracted during this review to determine the SMD of the respective oxidative stress marker post-acute exercise with supplementation compared to placebo. Within each study, the measurement period was consistent between the supplementation and placebo groups. Thus, this meta-analysis assesses the overall differences between supplementation and placebo as measured between the time periods immediately post exercise and 48 hours.

3.3.1 Malondialdehyde

A total of four studies were compared to establish the SMD of the impacts of supplementation of polyphenolic compounds has on post exercise MDA levels. One of the studies evaluated two separate types of polyphenolic compounds, which brought the total number of experiments to five to establish the SMD. The SMD for MDA was -1.34, CI between -1.86 and -0.82 μmol/L, and $P < 0.01$ (Appendix C, Figure 6). The data pertaining to MDA indicates supplementation decreases post-acute exercise MDA levels. The CI value indicates 95% of the time, the true population will fall between -1.86 and -0.82 μmol/L of acute exercise induced MDA levels when supplemented with polyphenolic compounds. There is sufficient evidence supporting the hypothesis there would be decrease in MDA post-acute exercise as a result of polyphenol supplementation.

3.4 Discussion

The aim of this review was to determine if the anti-oxidative properties of polyphenols could attenuate post-acute exercise oxidative stress. The results were relatively consistent in evaluating MDA oxidative stress marker levels. Both the type of polyphenol supplemented, and

the exercise protocol varied across all studies, which offered a range of support in the post-acute exercise anti-oxidative properties of polyphenol supplementation.

Oxidative stress is the most recognized explanation for the occurrence of muscle damage (Machado Á, da Silva, Souza, & Carpes, 2018). The exercise protocol used in the studies evaluated in this review lead to an imbalance of oxidative status resulting in the increase of oxidative stress. MDA is commonly used to measure for signs of oxidative stress, as they will rise after exercise dependent upon the type, duration, and intensity of exercise. It is involved in the lipid peroxidation process and are an important antioxidant agent and markers of an increased production of ROS.

An imbalance in the antioxidant system (protective mechanism) against ROS can lead to the damage of cellular molecules such as DNA, proteins, and lipids, which are considered the main targets of oxidative stress. Reactive oxygen species are typically produced in limited quantity within the human body. They are important compounds involved in regulating the processes involved in maintaining cell homeostasis and functions such as signal transduction, gene expression, and activation of receptors. Mitochondrial oxidative metabolism in cells produces ROS and organic peroxides during cell respiration. Furthermore, in hypoxic conditions, nitric oxide may also be produced during the respiratory chain reaction. Reactive nitrogen species (RNS) can further lead to the production of other reactive species (reactive aldehydes, malondialdehyde, and 4-hydroxynonenal). The prolonged overproduction of ROS/RNS can cause damage of the cellular structure and functions. Disproportionate production of ROS in cells and tissues can be harmful if not removed quickly. The damage to cells may become irreversible, leading to cell death by the necrotic and apoptotic processes (Hussain et al., 2016).

The anti-oxidative properties of polyphenols play a role in reducing ROS, which MDA is a marker of the product of ROS from lipid peroxidation. This is achieved through inhibiting oxidases, reduction of superoxide production, inhibiting oxidized cholesterol formation, stifling vascular smooth muscle cell proliferation and migration, the reduction of platelet aggregation, and improving mitochondrial oxidative stress.

The results of the individual studies evaluated during this review did differ dependent on the exercise protocol and type of polyphenol used in supplementation; however, in each case, oxidative stress was attenuated. The greatest impact supplementation had on MDA in this meta-analysis was with lippia citriodora extract (Carrera−Quintanar 2015) SMD −5.97 (Appendix C, Figure 7).

3.5 Conclusion

The evaluation of SMD data pertaining to the effects of supplementation of polyphenolic compounds on post-acute exercise oxidative stress markers was consistent. The levels of MDA showed a significant decrease with supplementation of polyphenolic compounds after acute exercise. Based on their respective SMD, we concluded that polyphenols supplementation decreased acute exercise-induced oxidative stress marker MDA.

CONCLUSION

Based on a statistical analysis for the SMD between supplementation and control groups of each study, we found: (1) Plasma CRP, IL-8 and TNF-α levels after acute exercise were not affected by polyphenols supplementation; (2) Plasma IL-6 and MDA levels after acute exercise were significantly lowered with polyphenols supplementation after acute exercise. Thus, we conclude polyphenols supplementation could reduce inflammatory marker IL-6 and oxidative stress marker MDA induced by acute exercises.

FUTURE DIRECTIONS

Further experimental research should be conducted to attempt to determine if polyphenols supplementation could reduce inflammatory marker IL-8 after acute exercise. Results in this study did not indicate there would be a reduction of post-acute exercise IL-8 inflammatory resulting from polyphenol supplementation, as IL-8 is only found in small amounts circulating in the blood stream after exercise. IL-8 is in locally contracted muscles and exerts its affects locally in the active muscle but not affecting your systemic inflammation. IL-8 is believed to be upregulated based on the duration and intensity of exercise. Therefore, experimental research with a longer duration of acute exercise with an intervention of polyphenol supplementation and muscle tissue biopsy samples rather than plasma blood samples should be done. Further evaluation of monetary commitment as well as resource availability would have to be evaluated prior to developing the research criteria, plan, and concept paper.

APPENDICIES

Appendix A: Glossary Terms

Aldehyde: Any of a class of organic compounds, wherein a carbon atom shares a double bond with an oxygen atom, a single bond with a hydrogen atom, and a single bond with another atom or group of atoms (Britannica, 2020).

Apoptosis: A mechanism allowing cells to self-destruct when stimulated by the appropriate trigger. In biology this is also known as "programmed cell death" (Britannica, 2020).

Classical Complement Pathway: The classical pathway is primarily activated by the binding of C1 to antigen-antibody complexes containing immunoglobins (IgM or IgG) (Medical-Dictionary, 2020).

Confidence Interval: Group of continuous or discrete adjacent values used to estimate statistical parameters (means or variance). CI's often include true values of the parameter a predetermined proportion of the time, should the process of finding the group of values be repeated a number of times (Merriam-Webster, 2020).

Cytokine: Various proteins secreted by cells involved in carrying signals to other cells nearby (Dictionary.Com, 2020).

Forest Plot: A graphical display intended to show the relative strength of treatment effects in various quantitative scientific studies addressing the same question (Definitions.net, 2020).

Free Radicals: Unstable molecules that can damage to cells in the human body. Free radicals form when atoms or molecules gain or lose electrons, and often occur as a result of the metabolic processes (Verywell Fit, 2020).

Granulocyte: Any group of white blood cells (basophil, eosinophil, or neutrophil) characterized by granule-containing cytoplasm and a lobed nucleus (Merriam-Webster, 2020).

Lipid Oxidation: A complex set of free radical reactions between fatty acids and oxygen, which results in oxidative degradation of lipids. This is also known as rancidity. Lipid oxidation free radicals (intermediate products) and reactive aldehydes (end products) can interact with other food constituents, such as proteins, sugars, pigments, and vitamins, and negatively modify their properties. The reaction mechanisms and rate of lipid oxidation is dependent on fatty acid composition, presence of prooxidants and antioxidants, type of lipid, and storage conditions (Mozuraityte, Kristinova, & Rustad, 2016).

Lymphocyte: Any of the colorless motile cells deriving from stem cells and differentiating in lymphoid tissue are the typical cellular elements of lymph, which includes the cellular mediators of immunity, and constitute 20-30% of the white blood cells of normal human blood (Merriam-Webster, 2020).

Macrophages: Specialized cells involved in detection, phagocytosis and destroying bacteria and other harmful organisms. Additionally, they introduce antigens to T cells and initiate inflammation by releasing cytokines (British Society for Immunology, 2020).

Messenger Ribonucleic Acid: Form of RNA mediating the transfer of genetic information from the cell nucleus to ribosomes in the cytoplasm, where it functions as a template for protein synthesis. It is created from a DNA template during the process of transcription (Medical-Dictionary, 2020).

Meta-Analysis: A statistical process combining the data of multiple studies to identify trends and common results (Dictionary.Com, 2020).

Natural Killer Cell: Characterized as cytolytic effector lymphocytes present in human peripheral blood. The "Natural Killer" name refers to the cell's ability to kill targets cells without requirement for a prior exposure to these targets (Vivier, 2006).

Neutrophils: A type of white blood cell that makes up 55-70 percent of white blood cells (Healthline, 2020).

Phagocytes: Type of cell with the ability to ingest at times digest foreign particles like bacteria, carbon, dust, and dye (Britannica, 2020).

Phagocytosis: The process where phagocytes ingest or engulf other cells or particles (Britannica, 2020).

Probability Value: Probability/likelihood of an outcome in a statistical experiment (Merriam-Webster, 2020).

Reactive Oxygen Species: An unstable molecule containing oxygen that easily reacts with other molecules in a cell. The buildup of ROS in cells can cause damage to DNA, RNA, and proteins. Additionally, ROS can cause cell death (National Cancer Institute, 2020).

Standard Mean Difference: Measure of statistical dispersion which is equal to the average absolute difference of two independent values derived from a probability distribution (Definitions.net, 2020).

Systemic Circulation: The circuit of vessels supplying oxygenated blood to tissues in the body and returning deoxygenated blood from the tissues of the body (Britannica, 2020).

Systematic Review: A review that attempts to identify, appraise, and synthesize all empirical evidence meeting pre-specified eligibility criteria. This process is to answer a specific research question using methods to minimize bias and produce reliable findings facilitating a well-informed decision-making process (Cochrane, 2020).

Appendix B: Acronyms

CI: Confidence Interval

CRP: C-Reactive Protein

HS-CRP: High-Sensitivity C-Reactive Protein

IL-6: Interleukin-6

IL-8: Interleukin-8

LIST: Loughborough Intermittent Shuttle Test

MDA: Malondialdehyde

P: Probability Value

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ROS: Reactive Oxygen Species

SMD: Standard Mean Difference

TNF-α: Tumor Necrosis Factor Alpha

Appendix C: Figures

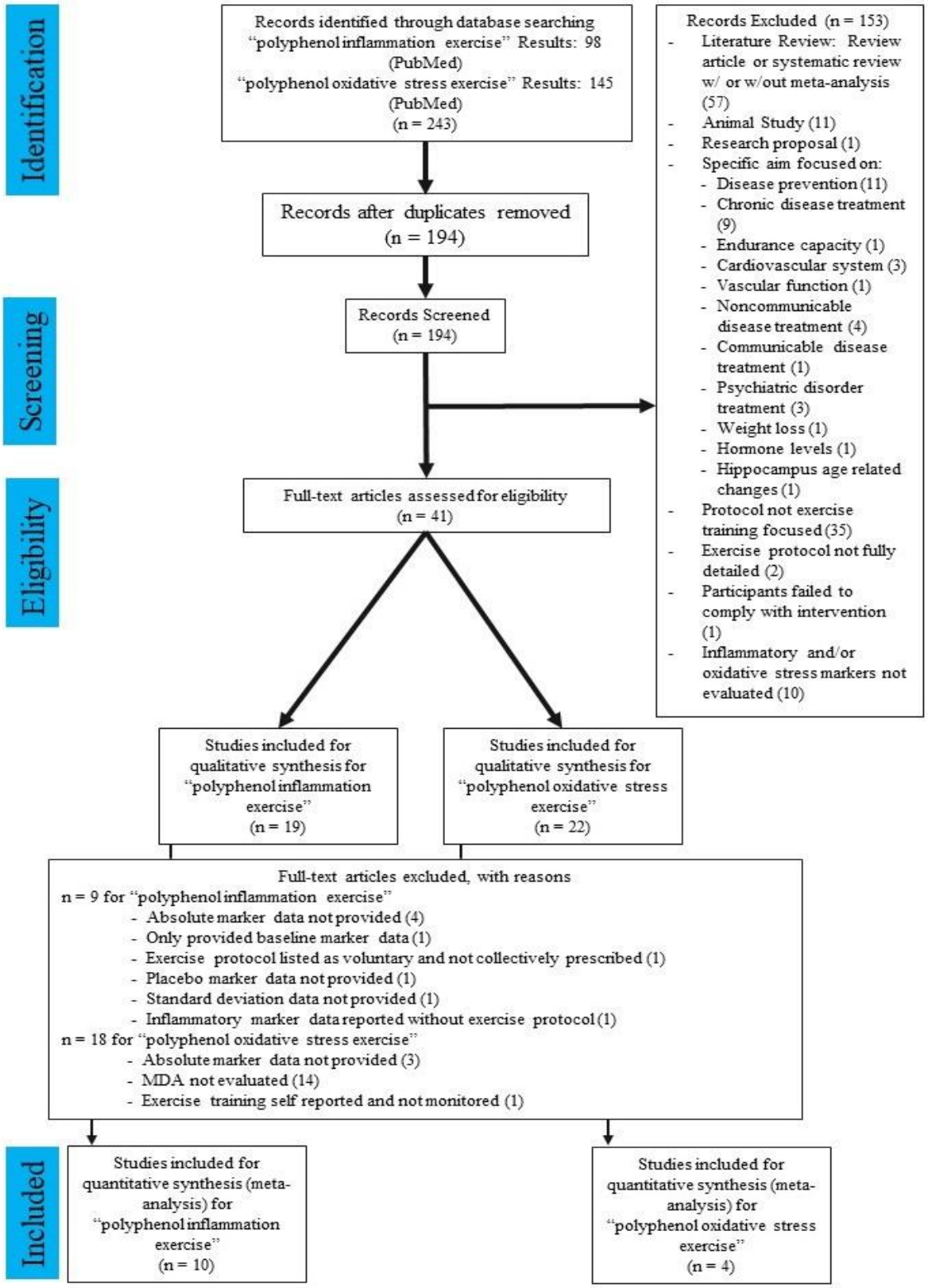

Figure 1: Flow Chart

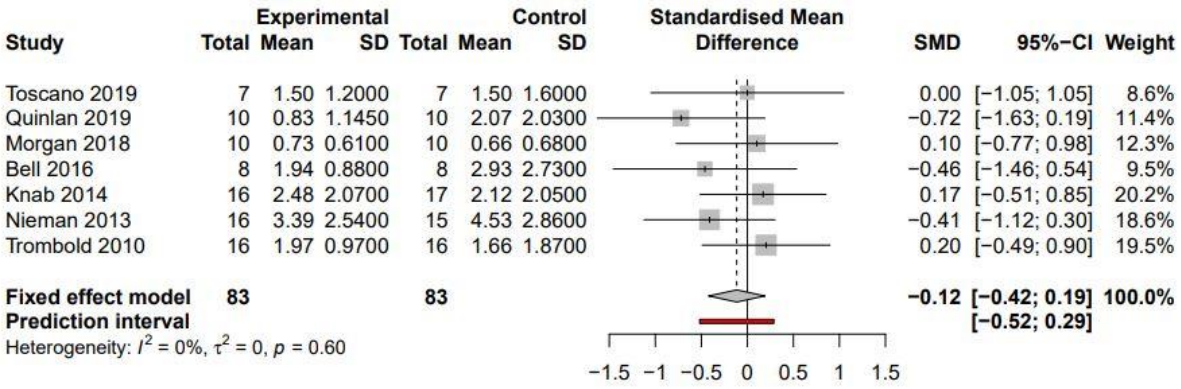

Figure 2: CRP Forest Plot

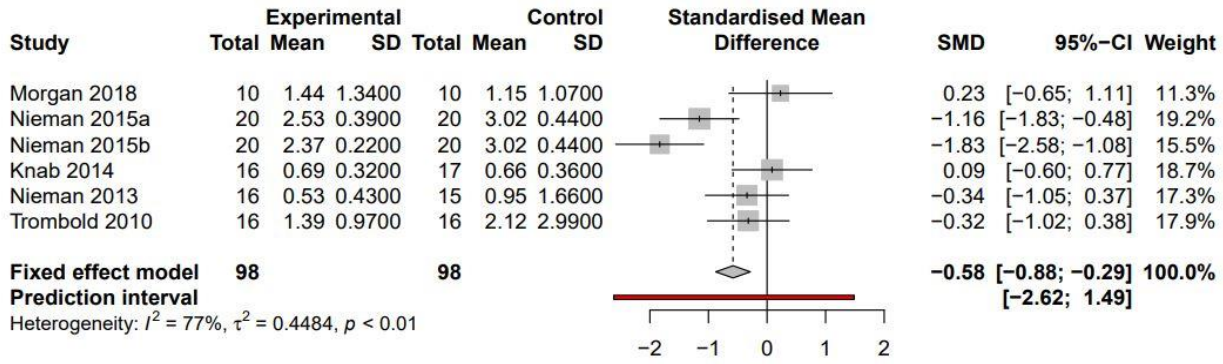

Figure 3: IL-6 Forest Plot

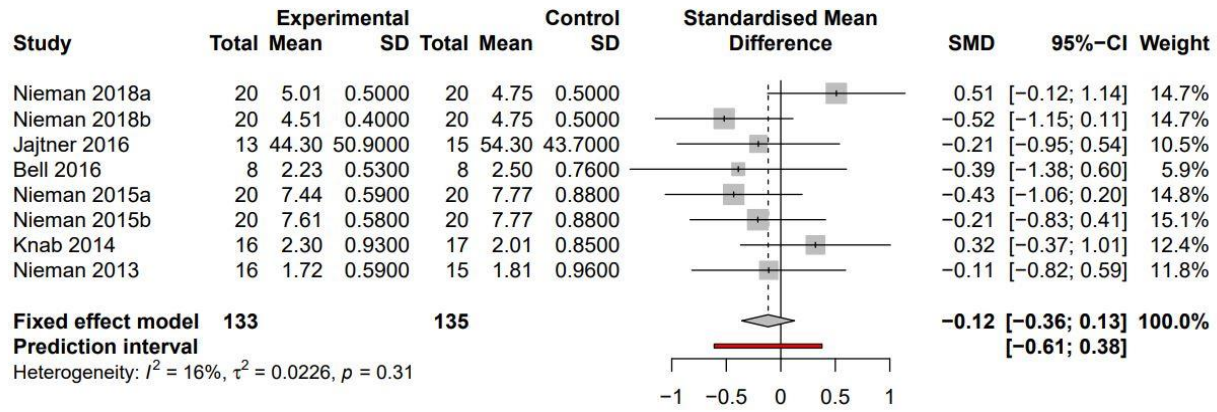

Figure 4: IL-8 Forest Plot

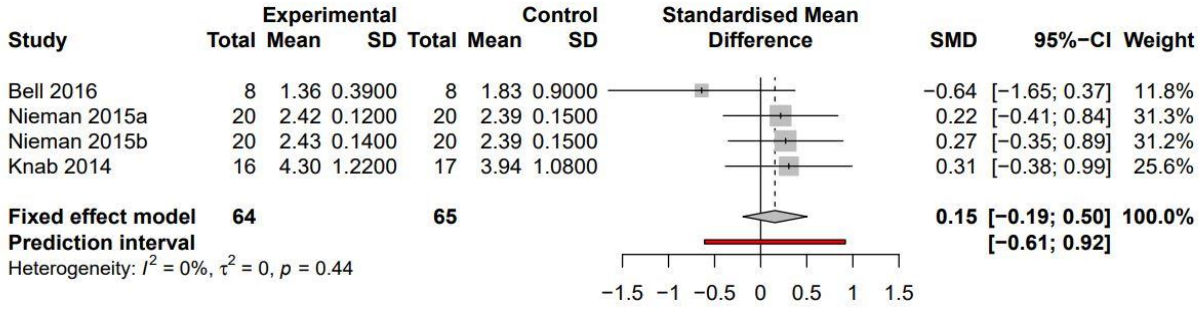

Figure 5: TNF-α Forest Plot

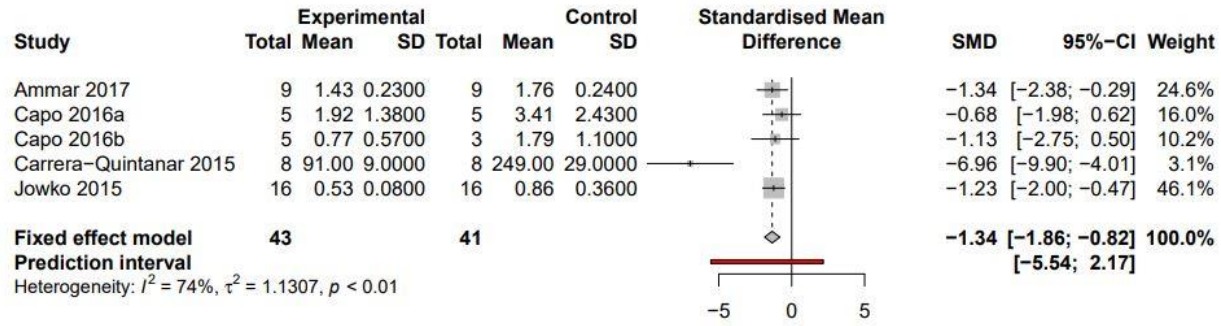

Figure 6: MDA Forest Plot

Appendix D: Tables

Table 1: Review Matrix for Impact of Polyphenol Supplementation on Inflammation After Acute Exercise

Review Matrix for Impact of Polyphenol Consumption on Inflammation After Acute Exercise					
Author/Year	**Article**	**Exercise**	**Intervention**	**Marker(s)**	**Results**
Toscano/2019	A Single Dose of Purple Grape Juice Improves Physical Performance and Antioxidant Activity in Runners: a Randomized, Crossover, Double-blind, Placebo Study	3200 m run to exhaustion	Consumption of grape juice	HS-CRP	HS-CRP (PLA 1.5 +/- 1.6 mg/dl; SUP 1.5 +/- 1.2 mg/dl)
Quinlan/2019	The Efficacy of Tart Cherry Juice in Aiding Recovery After Intermittent Exercise	Countermovement jump, 20m sprint, maximal voluntary isometric contraction	Supplementation with Tart Cherry Juice.	CRP	CRP (PLA 2.071 +/- 2.03 mg/L; SUP 0.831 +/- 1.145 mg/L)
Morgan/2018	Flavanol-Rich Cacao Mucilage Juice Enhances Recovery of Power but Not Strength from Intensive Exercise in Healthy, Young Men	Two trials of 10 sets of 10 single leg knee extensions at ~80% one repetition maximum	Supplementation with cacao juice	HS-CRP and IL-6	HS-CRP (PLA 0.66 +/- 0.68 mg/L; SUP 0.73 +/- 0.61 mg/L) and IL-6 (PLA 1.15 +/- 1.07 pg/mL; SUP 1.44 +/- 1.34 pg/mL)
Nieman/2018	Metabolic Recovery from Heavy Exertion Following Banana Compared to Sugar Beverage or Water Only Ingestion: A Randomized, Crossover Trial	Four 75-km cycling time trials	Supplementation with higher phenolic mini-yellow banana (a) and cavendish banana (b)	IL-8	IL-8 (PLA 4.75 +/- 0.5 pg/mL; SUP a 5.01 +/- 0.5 pg/mL, and SUP b 4.51 +/- 0.4 pg/mL)
Jajtner/2016	The Effect of Polyphenols on Cytokine and Granulocyte Response to Resistance Exercise	Resistance exercise session consisting of 6 sets of 10 repetitions of the squat as well as 4 sets of 10 repetitions of the leg press and leg extension exercises	Supplementation of proprietary polyphenol blend of water-extracted green and black tea (camellia sinensis)	IL-8	IL-8 (PLA 54.3 +/- 43.7 pg/mL; SUP 44.3 +/- 50.9 pg/mL)

Table 1: Continued

Author/Year	Article	Exercise	Intervention	Marker(s)	Results
Bell/2016	The Effects of Montmorency Tart Cherry Concentrate Supplementation on Recovery Following Prolonged, Intermittent Exercise	Adapted version of the Loughborough Intermittent Shuttle Test (12 x 20 m sprints w 10 m "stopping zone", 6 x 15 min, counter movement jump height, 20 m sprint time (20 m), and maximal voluntary isometric contraction of the knee extensors)	Supplementation of montmorency tart cherry.	HS-CRP, IL-8 and TNF-α	HS-CRP (PLA 2.93 +/- 2.73 pg/mL; SUP 1.94 +/- 0.88 pg/mL), IL-8 (PLA 2.5 +/- 0.76 pg/mL; SUP 2.23 +/- 0.53 pg/mL) and TNF-α (PLA 1.83 +/- 0.90 pg/mL; SUP 1.36 +/- 0.39 pg/mL)
Nieman/2015	Metabolomics-Based Analysis of Banana and Pear Ingestion on Exercise Performance and Recovery	Three 75-km cycling time trials	Consumption of water, bananas (a) and pears (b) (water only, bananas and water, and pears and water)	IL-6, IL-8 and TNF-α	IL-6 (PLA 3.02 +/- 0.44 pg/mL; SUP a 2.53 +/- 0.39 pg/mL; SUP b 2.37 +/- 0.22 pg/mL), IL-8 (PLA 7.77 +/- 0.88 pg/mL; SUP a 7.44 +/- 0.59 pg/mL; SUP b 7.61 +/- 0.58 pg/mL) and TNF-α (PLA 2.39 +/- 0.15 pg/mL; SUP a 2.42 +/- 0.12 pg/mL; SUP b 2.43 +/- 0.14 pg/mL)

Table 1: Continued

Author/Year	Article	Exercise	Intervention	Marker(s)	Results
Knab/2014	Effects of a Freeze-Dried Juice Blend Powder on Exercise-Induced Inflammation, Oxidative Stress, and Immune Function in Cyclists	During a 3-d period of intensified exercise, subjects cycled at 70%–75% VO2max for 2.25 h per day, followed by a 15-min time trial.	Supplementation of freeze-dried fruit and vegetable juice powder	CRP, IL-6, IL-8 and TNF-α	CRP (PLA 2.12 +/- 2.05 mg/L; SUP 2.48 +/- 2.07 mg/L), IL-6 (PLA 0.66 +/- 0.36 pg/mL; SUP 0.69 +/- 0.32 pg/mL), IL-8 (PLA 2.01 +/- 0.85 pg/mL; SUP 2.30 +/- 0.93 pg/mL) and TNF-α (PLA 3.94 +/- 1.08 pg/mL; SUP 4.30 +/- 1.22 pg/mL)
Nieman/2013	Influence of a Polyphenol-Enriched Protein Powder on Exercise-Induced Inflammation and Oxidative Stress in Athletes: A Randomized Trial Using a metabolomics approach	Subjects ran on treadmills for 2.5h at approximately 70% VO2max on three separate days.	Supplementation of polyphenol enriched protein powder.	CRP, IL-6 and IL-8	CRP (PLA 4.53 +/- 2.86 mg/dL; SUP 3.39 +/- 2.54 mg/dL), IL-6 (PLA 0.95 +/- 1.66 pg/mL; SUP 0.530 +/- 0.43 pg/mL) and IL-8 (PLA 1.81 +/- 0.96 pg/mL; SUP 1.72 +/- 0.59 pg/mL)
Trombold/2010	Ellagitannin Consumption Improves Strength Recovery 2-3 d After Eccentric Exercise	Two sets of 20 maximal eccentric elbow flexion repetitions starting with the elbow at 50 degrees of full flexion and ending at 170 degrees.	Supplementation of pomegranate extract	CRP and IL-6	CRP (PLA 1.66 +/- 1.87 ng/mL; SUP 1.97 +/- 0.97 ng/mL) and IL-6 (PLA 2.12 +/- 2.99 pg/mL; SUP 1.39 +/- 0.97 pg/mL)

Table 2: Review Matrix for Impact of Polyphenol Supplementation on Oxidative Stress After Acute Exercise

Review Matrix for Impact of Polyphenol Consumption on Oxidative Stress After Acute Exercise					
Author/Date	**Article**	**Exercise**	**Intervention**	**Marker(s)**	**Results**
Ammar/2017	Effects of Pomegranate Juice Supplementation on Oxidative Stress Biomarkers Following Weightlifting Exercise	Three Olympic Weightlifting exercises (snatch, clean and jerk, and squat) with five sets for each exercise. Specifically, participants completed 2 sets of 3 repetitions at 85% of 1-RM and 3 sets of 2 repetitions at 90% of 1-RM.	Consumption of pomegranate juice	MDA	MDA (PLA 1.76 +/- 0.24 µmol/L; and SUP 1.43 +/- 0.23 µmol/L)
Capo/2016	Effects of Dietary Almond and Olive Oil-Based Docosahexaenoic Acid and Vitamin E Enriched Beverage Supplementation on Athletic Performance and Oxidative Stress Markers	Continuously run on a treadmill at the speed of V60 for 5 minutes, V70 for 5 minutes and V80 for 5 minutes for three consecutive bouts with two minutes of recovery between bouts. Finally, the subjects ran at V90 until exhaustion	Supplementation with dietary almond- and olive oil based docosahexaenoic acid and vitamin E enriched beverage.	MDA	MDA (PLA Young 3.41 +/- 2.43 µmol/L and Senior 1.79 +/- 1.10 µmol/L; and SUP Young 1.92 +/- 1.38 µmol/L and Senior 0.77 +/- 0.57 µmol/L)
Carrera-Quintanar/2015	Effect of Polyphenol Supplements on Redox Status of Blood Cells: A Randomized Controlled Exercise Training Trial	Eccentric contraction-based resistance training routine for 60 min, 3 alternative days a week, for 3 weeks	Supplementation with lippia citriodora extract (commercially called PLX) acronym coming from ‘‘PoLyphenol eXtract’’	MDA	MDA (PLA 249 +/- 29 µmol/L; and SUP 91 +/- 9 µmol/L)

Table 2: Continued

Author/Year	Article	Exercise	Intervention	Marker(s)	Results
Jowko/2015	The Effect of Green Tea Extract Supplementation on Exercise Induced Oxidative Stress Parameters in Male Sprinters	Two repeated cycle sprint tests (RST; 4 9 15 s, with 1-min rest intervals)	Supplementation with green tea extract	MDA	MDA (PLA 0.86 +/- 0.36 µmol/L; and SUP 0.53 +/- 0.08 µmol/L)

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